Brumback
836576


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=> fil reg

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  conducting SmartSELECT searches.

=> e "cholesteryl-3.beta.-carboxamidoethylenetrimethylammonium iodide"/cn 5

E1            1     CHOLESTERYL VINYL SUCCINATE POLYMER/CN
E2            1     CHOLESTERYL-.BETA.-D-GLUCOSIDE-6-MONOPALMITATE/CN
E3            0 --> CHOLESTERYL-3.BETA.-CARBOXAMIDOETHYLENETRIMETHYLAMMONI
                    UM IODIDE/CN
E4            1     CHOLESTERYL-4-14C ARACHIDONATE/CN
E5            1     CHOLESTERYL-4-14C LINOLEATE/CN

=> s ?carboxamidoethylenamine?/cns

L1            0 ?CARBOXAMIDOETHYLENAMINE?/CNS

=> s ?oxysuccinamidoethylene?/cns

L2            0 ?OXYSUCCINAMIDOETHYLENE?/CNS

=> s ?"dimethylaminoethane)carbamoyl]cholester"?/cns

              6 ?"DIMETHYLAMINOETHANE"/CNS
          13797 "CARBAMOYL"/CNS
           1584 "CHOLESTER"?/CNS
L3            0 ?"DIMETHYLAMINOETHANE)CARBAMOYL]CHOLESTER"?/CNS
                  ((?"DIMETHYLAMINOETHANE"(W)"CARBAMOYL"(W)"CHOLESTER"?)/C
                  NS)

=> fil ca,caplus

FILE 'CA' ENTERED AT 16:15:26 ON 15 DEC 1997
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FILE 'CAPLUS' ENTERED AT 16:15:26 ON 15 DEC 1997
                        Searcher  :  Shears   308-4994
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=> d que

L4 (2952)SEA CHOLESTER?(S)(3(W)(BETA OR B))
L5 49 SEA L4(S)(CARBAM? OR CARBOXAMID? OR CARBOX? AMID?)

=> dup rem l5

PROCESSING COMPLETED FOR L5
L6 25 DUP REM L5 (24 DUPLICATES REMOVED)

=> d 1-25 .bevstr1

L6 ANSWER 1 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 1
AN 127:298774 CA
TI Spray-dried microparticles as therapeutic vehicles for use in gene therapy
IN Sutton, Andrew Derek; Ogden, Jill Elizabeth; Johnson, Richard Alan
PA Andaris Ltd., UK; Sutton, Andrew Derek; Ogden, Jill Elizabeth; Johnson, Richard Alan
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
PI WO 9736578 A1 971009
DS W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 97-GB953 970403
PRAI GB 96-7035 960403
WO 96-GB1379 960607
DT Patent
LA English
AB Microparticles, which are smooth and spherical, and at least 90 % of which have a vol. median particle size of 1 to 10 .mu.m, comprise a substantially uniform mixt. of an agent for gene therapy and an excipient. For example, a naked or encapsulated gene can thus be administered, using a dry powder inhaler. A plasmid pCMV promoter:luciferase gene was reconstituted with **3**. **beta**.-[N-(N,N-dimethylaminoethyl)**carbamoyl**] **cholesterol**/dioleoylphosphatidylethanolamine at a charge ratio of 5:1 and spray dried.
IT Encapsulation

Gene therapy
Inhalants (drug delivery systems)
Inhalers (medical)
Microparticles (drug delivery systems)
Particle size
Spray drying
Virus
(spray-dried microparticles as therapeutic vehicles for gene therapy)

IT Carbohydrates, biological studies
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(spray-dried microparticles as therapeutic vehicles for gene therapy)

IT DNA
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(spray-dried microparticles as therapeutic vehicles for gene therapy)

IT Genes (animal)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(spray-dried microparticles as therapeutic vehicles for gene therapy)

IT 57-50-1, Sucrose, biological studies 63-42-3, Lactose 87-78-5, Mannitol
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(spray-dried microparticles as therapeutic vehicles for gene therapy)

L6 ANSWER 2 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 2
AN 127:144710 CA
TI Intratumoral pharmacokinetics and in vivo gene expression of naked plasmid DNA and its cationic liposome complexes after direct gene transfer
AU Nomura, Takehiko; Nakajima, Shin; Kawabata, Kenji; Yamashita, Fumiyoshi; Takakura, Yoshinobu; Hashida, Mitsuru
CS Department Drug Delivery Research, Faculty Pharmaceutical Sciences, Kyoto University, Kyoto, 606-01, Japan
SO Cancer Res. (1997), 57(13), 2681-2686
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The pharmacokinetic properties and gene expression of naked plasmid DNA and its cationic liposome complexes were studied after direct

intratumoral injection. Using a Walker 256 tissue-isolated tumor perfusion system, we quantified the recovery of naked plasmid DNA and cationic liposome complexes in the tumor, leakage from the tumor surface, and the venous outflow after intratumoral injection. Approx. 50% of naked plasmid DNA had been eliminated from the tumor 2 h after injection, whereas more than 90% of plasmid DNA was retained in the tumor when it was complexed with cationic liposomes. However, the distribution of these complexes in the tumor was restricted to the tissue surrounding the injection site. Pharmacokinetic anal. of the venous outflow profiles suggested that the rate-limiting process that dets. the retention of plasmid DNA in the tumor is transferred from the injection site in the tumor tissue and that complexation with cationic liposomes may retard this process. Furthermore, we examd. the gene expression of chloramphenicol acetyltransferase DNA constructs (naked pCMV-CAT) and the corresponding cationic liposome [**3**,.**beta**.-(N,-(N',N'-dimethylaminoethane)**carbamoyl**) **cholesterol**] complexes. A similar level of gene expression was obsd. in vivo after direct intratumoral injection of naked DNA and its cationic liposome complexes. In both cases, a great variation was obsd. between tumors, and localization of gene-transduced cells in the tumor tissue was limited to the area in the vicinity of the injection site. Thus, these pharmacokinetic and gene expression studies have demonstrated that cationic liposomes can enhance the retention of injected DNA in the tumor model, whereas cationic liposome complex does not necessarily improve gene expression because of its poor dissemination in this tumor. The present study also suggested that there is a need to control the behavior of the injected naked plasmid DNA and its cationic liposome complexes to ensure better distribution throughout the tumor.

IT Antitumor agents
Gene therapy
Liposomes (drug delivery systems)
Plasmids
(pharmacokinetics and gene expression of naked plasmid DNA and its cationic liposome complexes in Walker 256 tumor)

IT DNA
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetics and gene expression of naked plasmid DNA and its cationic liposome complexes in Walker 256 tumor)

IT 9040-07-7, Chloramphenicol acetyltransferase 137056-72-5
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetics and gene expression of naked plasmid DNA and its cationic liposome complexes in Walker 256 tumor)

L6 ANSWER 3 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 3
AN 127:70715 CA

TI Optimization of liposome mediated transfection of a neuronal cell line

AU Mcquillin, Andrew; Murray, Karl D.; Etheridge, Christopher J.; Stewart, Luisa; Cooper, Robert G.; Brett, Peter M.; Miller, Andrew D.; Gurling, Hugh M. D.

CS Molecular Psychiatry Laboratory, Department of Psychiatry and Behavioural Sciences, Windeyer Institute of Medical, UCL Medical School, London, W1P 6DB, UK

SO NeuroReport (1997), 8(6), 1481-1484
CODEN: NERPEZ; ISSN: 0959-4965

PB Rapid Science Publishers

DT Journal

LA English

AB A cell line derived from sensory neurons was transfected with high efficiency using cationic liposomes, formulated from **3**. **beta**.-[N-(N',N'-dimethylaminoethyl)**carbamoyl**] **cholesterol** (DC-Chol) and dioleoyl L-.alpha.-phosphatidylethanolamine (DOPE). This is the first time that cationic liposomes of this type have been reported to transfect a neuronal cell line. We used a reporter gene construct expressing .beta.-galactosidase under the control of the cytomegalovirus immediate early promoter and routinely obsd. transfection efficiencies >40%. Parameters affecting transfection efficiency were examd. and the ratio of DNA to liposome proved to be crucial. Liposome formulation procedures and cell transfection protocols devised here will be used as a basis for further in vivo and in vitro work.

IT Animal cell line
(ND7; optimization of liposome mediated transfection of a neuronal cell line)

IT Cytomegalovirus
Gene therapy
Liposomes (drug delivery systems)
Neurons
Transformation (genetic)
(optimization of liposome mediated transfection of a neuronal cell line)

IT DNA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of liposome mediated transfection of a neuronal cell line)

IT 4004-05-1, Dioleoylphosphatidylethanolamine 137056-72-5
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(optimization of liposome mediated transfection of a neuronal cell line)

L6 ANSWER 4 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 4
Searcher : Shears 308-4994

AN 127:76698 CA
TI Transfection of avian LMH-2A hepatoma cells with cationic lipids
AU Walzem, R. L.; Hickman, M. A.; German, J. B.; Hansen, R. J.
CS Departments of Molecular Biosciences, School of Veterinary Medicine, University of California-Davis, Davis, CA, 95616, USA
SO Poult. Sci. (1997), 76(6), 882-886
CODEN: POSCAL; ISSN: 0032-5791
PB Poultry Science Association, Inc.
DT Journal
LA English
AB LMH-2A is an estrogen-responsive avian hepatoma cell line whose susceptibility to cationic-lipid-mediated transfection is poorly described. **3.beta.**[N-N',N'-(dimethylaminoethane)-**carbamoyl**]**cholesterol** (DCC) requires a one-step synthesis, and can be used to formulate transfection-grade liposomes when combined with dioleoylphosphatidylethanolamine (DOPE) 1/1 (wt./wt.). Luciferase activities in LMH-2A cells were 8.5-fold and 87.5-fold greater than those in HepG2 and FTO2B cells, resp., following DCC-liposome-mediated transfection with a reporter consisting of the human cytomegalovirus immediate-early promoter (CMV), joined to Photinus pyralis luciferase (L) cDNA, designated pCMVL. Using pCMVL, N-(2-bromoethyl)-N,N-dimethyl-2,3-bis(9-octadecenyloxy)-propanaminimun bromide (BMOP)/DOPE 1/1 (wt./wt.), at a 7.5:1 ratio with DNA, produced luciferase activities that were 2.9-fold higher than those of DCC-liposomes, at an optimal 10:1 lipid:DNA ratio. At optimal lipid:DNA ratios, com. available liposomes, Transfectam.RTM. Lipofectamine.RTM., and Lipofectin.RTM. produced luciferase activities that were 1.39, 1.03, and 0.47-fold those of DCC-liposomes. The effect of 0, 10, 100, or 500 nM/L 17.beta.-estradiol on the expression of pCMVL and a second luciferase reporter contg. the -593/+48 promoter region of the estrogen-responsive avian apo VLDL-II gene, designated pApoL, was tested in cells cultured in the presence or absence of 10% chicken serum. The CMV promoter supported a high level of expression in LMH-2A cells that was unaffected by serum alone, but was weakly responsive to estrogen. Estrogen responses of both reporters reached a plateau at 10 nM/L. Estrogen increased the expression of pApoL 24-fold and 79-fold in the absence and presence of serum, resp. The -593/+48 region of the apo VLDL-II promoter may not contain previously reported neg. insulin response elements, but chicken serum contains factors that enhance estrogen responsiveness of this region.
IT Animal cell line
(LMH-2A; transfection of avian LMH-2A hepatoma cells with cationic lipids)
IT Liposomes
(cationic; transfection of avian LMH-2A hepatoma cells with cationic lipids)

IT Plasmid vectors
(pCMVL and pApoL; transfection of avian LMH-2A hepatoma cells with cationic lipids)
IT Transformation (genetic)
(transfection of avian LMH-2A hepatoma cells with cationic lipids)
IT 50-28-2, 17.beta.-Estradiol, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estrogen responsiveness of expression; transfection of avian LMH-2A hepatoma cells with cationic lipids)
IT 137056-72-5 156180-28-8
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(transfection of avian LMH-2A hepatoma cells with cationic lipids)

L6 ANSWER 5 OF 25 CAPLUS COPYRIGHT 1997 ACS
AN 1997:646908 CAPLUS
TI Physicochemical properties and in vitro toxicity of cationic liposome cDNA complexes
AU Schreier, Hans; Gagne, Lucie; Bock, Thomas; Erdos, Gregory W.; Druzgala, Pascal; Conary, Jon T.; Mueller, Bernd W.
CS Advanced Therapies Inc., Suite 210A, 371 Bel Marin Keys, Novato, CA, 94949, USA
SO Pharm. Acta Helv. (1997), 72(4), 215-223
CODEN: PAHEAA; ISSN: 0031-6865
PB Elsevier
DT Journal
LA English
AB The purpose of this study was to elucidate the interaction of cationic liposomes and plasmid cDNA by examg. their ultrastructure, zeta potential, stability in aq. media and protection from DNaseI digestion; their potential for hemolysis and platelet aggregation was evaluated as it may serve as an in vitro toxicity screen. Liposomes consisting of N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) or **3.beta**.-[N-(N',N'-dimethylaminoethane)-**carbamoyl**]-**cholesterol** (DC-Chol) and dioleylphosphatidylethanolamine (DOPE) were complexed with plasmid constructs of ovine prostaglandin G/H synthase (pCMV4-PGH) or human .alpha.1-antitrypsin (pCMV4-AAT) at lipid:plasmid (L/P) ratios of 3:1-8:1 (wt./wt.). The electron micrographs showed bead-like attachment of liposomes to cDNA and coating of plasmid strands. The zeta potential showed isoelec. points at L/P ratios of 3.5-4 (DOTMA/DOPE) and 5.5-6.5, corresponding to a pKa of 6.45 (DC-Chol/DOPE). Liposome cDNA complexes were stable in water, saline and 5% dextrose for 48 h, but pptd. instantaneously in PBS. An increase in the L/P ratio corresponded with increased protection from DNaseI digestion.

DOTMA/DOPE liposomes alone were highly hemolytic and DC-Chol/DOPE liposomes moderately hemolytic; hemolysis was abolished by cDNA complexation, with the exception of very high (.gtoreq.7:1) L/P ratios. Both liposomes alone and cDNA complexes caused transient serum turbidity, while none caused platelet aggregation. It was concluded that current cationic lipid cDNA formulations are metastable and appear to have very little if any toxicity with respect to hemolytic potential and untoward interaction with other blood components. The results are discussed in relation to the use of cationic liposomal formulations to deliver plasmid vectors in gene therapy.

IT Drug toxicity
Gene therapy
Liposomes (drug delivery systems)
Plasmid vectors
(physicochem. properties and in vitro toxicity of cationic liposome cDNA complexes in relation to delivery of plasmid vectors in gene therapy)

IT cDNA
RL: ADV (Adverse effect, including toxicity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(physicochem. properties and in vitro toxicity of cationic liposome cDNA complexes in relation to delivery of plasmid vectors in gene therapy)

IT 4004-05-1, DOPE 104162-48-3, DOTMA 137056-72-5
RL: ADV (Adverse effect, including toxicity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(physicochem. properties and in vitro toxicity of cationic liposome cDNA complexes in relation to delivery of plasmid vectors in gene therapy)

L6 ANSWER 6 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 5
AN 127:298617 CA
TI Electrostatic parameters of cationic liposomes commonly used for gene delivery as determined by 4-heptadecyl-7-hydroxycoumarin
AU Zuidam, Nicolaas J.; Barenholz, Yechezkel
CS Department of Biochemistry, The Hebrew University, Hadassah Medical School, P.O. Box 12272, Jerusalem, Israel
SO Biochim. Biophys. Acta (1997), 1329(2), 211-222
CODEN: BBACAQ; ISSN: 0006-3002
PB Elsevier
DT Journal
LA English
AB Cationic liposomes are used to deliver genes into cells in vitro and in vivo. The present study is aimed to characterize the electrostatic parameters of cationic, large unilamellar vesicles, 110.+-.20 nm in size, composed of DOTAP/DOPE (mole ratio 1/1), DOTAP/DOPC (mole ratio 1/1), 100% DOTAP, DMRIE/DOPE 1/1, or DC-CHOL/DOPE (mole ratio 1/1). {Abbreviations: DOTAP,

N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphatidylethanolamine; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine; DMRIE, 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethylammonium bromide; DC-CHOL, **3.beta.**[N-(N',N'-dimethylaminoethane) **carbamoyl]cholesterol**}. The cationic liposomes had a large pos. surface potential and a high pH at the liposomal surface in 20 mM Hepes buffer (pH 7.4) as monitored by the pH-sensitive fluorophore 4-heptadecyl-7-hydroxycoumarin. In contrast to DOTAP and DMRIE which were 100% charged, DC-CHOL in DC-CHOL/DOPE (1/1) liposomes was only about 50% charged in 20 mM Hepes buffer (pH 7.4). This might result in an easier dissocn. of bilayers contg. DC-CHOL from the plasmid DNA (which is necessary to enable transcription), in a decrease of the charge on the external surfaces of the liposomes or DNA-lipid complexes, and in an increase in release of the DNA-lipid complex into the cytosol from the endosomes. Other electrostatic characteristics found were that the primary amine group of DOPE in cationic liposomes dissocd. at high (>7.9) pHbulk and that a salt bridge was likely between the quaternary amine of DOTAP or DMRIE and the phosphate group of DOPE or DOPC, but not between the tertiary amine of DC-CHOL and the phosphate group of DOPE. The liposomes contg. DOTAP were unstable upon diln., probably due to the high crit. aggregation concn. of DOTAP, 7.times.10-5 M. This might also be a mechanism of the dissocn. of bilayers contg. DOTAP from the plasmid DNA.

IT Liposomes (drug delivery systems)
(cationic; electrostatic parameters of cationic liposomes commonly used for gene delivery as detd. by 4-heptadecyl-7-hydroxycoumarin)

IT Gene therapy
Genetic engineering
(electrostatic parameters of cationic liposomes commonly used for gene delivery as detd. by 4-heptadecyl-7-hydroxycoumarin)

IT Electricity
(electrostatics; electrostatic parameters of cationic liposomes commonly used for gene delivery as detd. by 4-heptadecyl-7-hydroxycoumarin)

IT 4004-05-1, 1,2-Dioleoyl-sn-glycero-3-phosphatidylethanolamine
4235-95-4 132172-61-3 137056-72-5 153312-64-2
RL: DEV (Device component use); PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process); USES (Uses)
(electrostatic parameters of cationic liposomes commonly used for gene delivery as detd. by 4-heptadecyl-7-hydroxycoumarin)

L6 ANSWER 7 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 6
AN 127:131699 CA
TI Gene transfection by cationic liposomes: comparison of the transfection efficiency of liposomes prepared from various positively charged lipids

AU Zhao, Dan-Dan; Watarai, Shinobu; Lee, Jin-Tae; Kouchi, Shuuichi; Ohmori, Hitishi; Yasuda, Tatsuji
CS Department of Cell Chemistry, Institute of Cellular and Molecular Biology, Okayama University Medical School, Okayama, 700, Japan
SO Acta Med. Okayama (1997), 51(3), 149-154
CODEN: AMOKAG; ISSN: 0386-300X
PB Okayama University Medical School
DT Journal
LA English
AB We compared the transfection efficiency of four types of pos. charged liposomes composed of (i) N-(.alpha.-trimethylammonioacetyl)-didodecyl-D-glutamate chloride (TMAG), dilauroylphosphatidylcholine (DLPC), and dioleoylphosphatidylethanolamine (DOPE) (1:2:2 molar ratio); (ii) **3.beta.** [N-(N', N'-dimethylaminoethane)-**carbamoyl**] **cholesterol** (DC-Chol) and DOPE (3:2 molar ratio); (iii) dimethyldioctadecylammonium bromide (DDAB) and DOPE (1:2.2 molar ratio); (i.v.) N-[1- (2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride (DOTMA) and DOPE (1: 1, wt./wt.; lipofectin). Luciferase gene was used as a reporter gene. Among the cationic liposomes used, the liposomes composed of TMAG, DOPE and DLPC showed a much higher efficiency of plasmid DNA entrapment than the other cationic liposomes tested. In the absence of serum, the cationic multilamellar vesicles (MLV) and small unilamellar vesicles (SUV) composed of TMAG, DOPE and DLPC gave highly efficient transfection. MLV, dehydration-rehydration vesicles (DRV), and SUV liposomes prepd. with the mixts. of DC-Chol and DOPE showed similar levels of transfection efficiency. However, the cationic liposomes composed of DDAB and DOPE showed inferior efficiency, whether in the form of DRV, SUV or MLV. The transfection efficiency of lipofectin was also low. In the presence of serum, a considerable (about 30-50%) amt. of transfection activity was still obsd. at 10% fetal calf serum in the cationic MLV and SUV composed of TMAG, DOPE and DLPC. Cationic MLV, composed of TMAG, DOPE and DLPC, can transfect plasmid DNA, not only in the adherent cell lines but also in the suspension cell lines. These findings indicate that the transfection efficiency of cationic liposomes is affected by the lipid compn., the type of liposome, or the presence or absence of serum. They also indicate that the cationic liposomes contg. TMAG, DOPE and DLPC are efficient vectors for gene transfer into cells.
IT Liposomes
(cationic; gene transfection by cationic liposomes: comparison of transfection efficiency of liposomes prepd. from various pos. charged lipids)
IT Transformation (genetic)
(liposome-mediated; gene transfection by cationic liposomes: comparison of transfection efficiency of liposomes prepd. from various pos. charged lipids)
IT Genes

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(transfer of,; gene transfection by cationic liposomes: comparison of transfection efficiency of liposomes prepd. from various pos. charged lipids)

IT 18194-25-7, Dilauroylphosphatidylcholine
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(gene transfection by cationic liposomes and comparison of transfection efficiency of liposomes prepd. from various pos. charged lipids)

IT 2462-63-7, Dioleoylphosphatidylethanolamine 131897-06-8, N-(.alpha.-Trimethylammonioacetyl)-didodecyl-D-glutamate chloride
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(gene transfection by cationic liposomes: comparison of transfection efficiency of liposomes prepd. from various pos. charged lipids)

L6 ANSWER 8 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 7
AN 127:2669 CA
TI Lipid-mediated transfection of normal adult human hepatocytes in primary culture
AU Ourlin, Jean Claude; Vilarem, Marie-Jose; Daujat, Martine; Harricane, Marie-Cecile; Domergue, Jacques; Joyeux, Henri; Baulieux, Jean; Maurel, Patrick
CS INSERM U-128, CNRS, Montpellier, 34033, Fr.
SO Anal. Biochem. (1997), 247(1), 34-44
CODEN: ANBCA2; ISSN: 0003-2697
PB Academic
DT Journal
LA English
AB The aim of this work was to develop a procedure for the lipid-mediated transfection of DNA into normal adult human hepatocytes in culture. Cells were plated in a serum-free culture medium at various cell densities, on plastic or collagen-coated dishes, both in the absence and in the presence of epidermal growth factor (EGF). The cells were incubated for various periods of time with mixts. of DNA-lipofectin or DNA-**3.beta**.[N-(N',N'-dimethylaminoethane)-**carbamoyl**] **cholesterol** (DC-chol) liposomes, and the efficiency of transfection was assessed by measuring the activity of reporter genes, .beta.-galactosidase or chloramphenicol acetyltransferase (CAT). For comparison, similar expts. were carried out with human cell lines including HepG2, Caco-2, and WRL68. The efficiency of transfection (in percentage of cells) was not significantly different after transfection with lipofectin or DC-chol and

comprised between 0.04 and 1.7% (extreme values) for different cultures. The efficiency of transfection decreased as the age or d. of the culture increased and increased in cultures treated with EGF. Direct measurement of the rate of DNA synthesis suggested that the efficiency of transfection was related to the no. of cells entering the S phase. Under the same conditions, the efficiency of transfection was 1-2 orders of magnitude greater in the 3 cell lines. A plasmid harboring 660 bp of the 5'-flanking region of CYP1A1 (contg. two xenobiotic enhancer elements) fused upstream of the promoter of thymidine kinase and the CAT reporter gene was constructed. When this plasmid was transfected in human hepatocytes, CAT activity was induced as expected. We conclude that normal adult human hepatocytes can be transfected with exogenous DNA and that the transfected construct is regulated in the manner expected from in vivo studies.

IT DNA
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
([(dimethylaminoethane)carbamoyl]cholesterol complexes; lipid-mediated transfection of normal adult human hepatocytes in primary culture)

IT Hepatocyte
Liposomes
Plasmids
Primary tissue culture (animal)
Transformation (genetic)
(lipid-mediated transfection of normal adult human hepatocytes in primary culture)

IT Lipids, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(lipid-mediated transfection of normal adult human hepatocytes in primary culture)

IT 62229-50-9, Epidermal growth factor 128835-92-7, Lipofectin 137056-72-5D, DNA complexes
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(lipid-mediated transfection of normal adult human hepatocytes in primary culture)

L6 ANSWER 9 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 8
AN 126:122476 CA
TI Cationic lipid acid salt of **3.beta**.-[N-(N,N-dimethylaminoethyl)**carbamoyl**]**cholesterol**
IN Wyse, Joseph W.; Warner, Charles D.
PA Aronex Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
PI WO 9640067 A1 961219

DS W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 96-US9954 960607
PRAI US 95-485866 950607
DT Patent
LA English
AB This invention discloses a novel cationic lipid acid salt of **3.beta.**-[N-(N,N-dimethylaminoethyl) **carbamoyl]cholesterol** (I). Also disclosed is a transmembrane compatible body suitable for transfection of animals and animal cells with nucleotides such as DNA, RNA, and synthetic nucleotides. Such transmembrane compatible bodies arise from hydratable non-liposomal halogenated solvent-free lyophilizate comprising I and DOPE. This invention yet further discloses a halogenated solvent-free aq. soln., suitable for lyophilization into a preliposomal powder, wherein the soln. comprises I wherein substantially all I is dissolved.
IT DNA
Gene therapy
Liposomes (drug delivery systems)
Nucleotides, biological studies
RNA
Transformation (genetic)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic lipid acid salt of dimethylaminoethylcarbamoyl cholesterol)
IT 137056-72-5P 166023-21-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cationic lipid acid salt of dimethylaminoethylcarbamoyl cholesterol)
IT 50-99-7, D-Glucose, biological studies 57-50-1, Sucrose, biological studies 58-86-6, D-Xylose, biological studies 63-42-3 69-65-8, D-Mannitol 2462-63-7, Dioleoylphosphatidylethanolamine 3458-28-4, D-Mannose 68737-67-7, Dioleoylphosphatidylcholine
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic lipid acid salt of dimethylaminoethylcarbamoyl cholesterol)
IT 108-00-9, N,N-Dimethylethylenediamine 7144-08-3, Cholesteryl chloroformate
RL: RCT (Reactant)
(cationic lipid acid salt of dimethylaminoethylcarbamoyl cholesterol)

L6 ANSWER 10 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 9
AN 125:96041 CA

TI Adjuvant for vaccines comprising a sterol-derived lipophilic group bound to a cationic group

IN Haensler, Jean; Trannoy, Emmanuelle; Ronco, Jorge
PA Pasteur Merieux Serums et Vaccins, Fr.

SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
PI WO 9614831 A1 960523
DS W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR1495 951114
PRAI FR 94-13606 941114
DT Patent
LA French

AB An amphipathic compd. including a sterol-derived lipophilic grouping bound to a cationic grouping for use as an adjuvant in the delivery of a vaccine compn. In a particular embodiment, the lipophilic grouping is a cholesterol deriv. and the cations grouping is a quaternary ammonium or a protonable amine. A vaccine compn. including one or more antigens with at least one amphipathic compd. having a sterol-derived lipophilic grouping bound to a cationic grouping, is also disclosed. A soln. of 2.25 g **cholesteryl** chloroformate in 5 mL chloroform was stirred with a soln. of 2 mL N,N-dimethylethylenediamine in 3 mL chloroform at 0.degree. followed by evapn. of the solvent and the purifn. of **3.beta**.-[N-(N'N'-dimthylaminoethane)-**carbamoyl**]-**cholesterol** (I) by recrystn. Thus, 300 mg I was dissolved in 100 .mu.L ethanol and 75 .mu.L of this soln was injected to 3 mL of water at 45.degree. and stirred for 5 min. The micellar suspension thus obtained was mixed with 200 .mu.L of a monovalent influenza vaccine and divided in 0.3 mL doses. The immunol. response of guinea pigs to the above vaccine was studied.

IT Vaccines
Lipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvant for vaccines comprising sterol-derived lipophilic group bound to cationic group)

IT Quaternary ammonium compounds, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(conjugates with sterols; adjuvant for vaccines comprising sterol-derived lipophilic group bound to cationic group)

IT Virus, animal
(influenza, adjuvant for vaccines comprising sterol-derived lipophilic group bound to cationic group)

IT Pharmaceutical dosage forms
(liposomes, adjuvant for vaccines comprising sterol-derived lipophilic group bound to cationic group)

IT 108-00-9, N,N-Dimethylethylenediamine 7144-08-3, Cholesteryl chloroformate
RL: RCT (Reactant)
(adjuvant for vaccines comprising sterol-derived lipophilic group bound to cationic group)
IT 137056-72-5P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(adjuvant for vaccines comprising sterol-derived lipophilic group bound to cationic group)
IT 2462-63-7 10015-85-7, Dioleoyl phosphatidylcholine 123628-75-1 144108-36-1 154440-71-8 178823-15-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvant for vaccines comprising sterol-derived lipophilic group bound to cationic group)

L6 ANSWER 11 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 10
AN 125:134786 CA
TI Cholesterol (dimethylaminoethane)carbamoyl deriv. preparation and use for liposome-mediated gene transfer
IN Reszka, Regina
PA Max-Delbrueck-Centrum fuer Moledulare Medizin, Germany
SO Ger. Offen., 5 pp.
CODEN: GWXXBX
PI DE 4446937 A1 960704
AI DE 94-4446937 941228
DT Patent
LA German
AB A new cholesterol deriv. for liposome-mediated gene transfer was prepd. and has applications in medicine and gene transfer. The **cholesterol** deriv., **3.beta**.-[N-(N,N'-dimethylaminoethane)**carbamoyl**] **cholesterol** (DAC-Chol), was prepd. from reaction of N,N'-dimethylethylenediamine and chloroformate **cholesterol** in equal amts. and purified by chromatog. DAC-Chol is not toxic and can be used for direct liposome-mediated gene transfer. A new method for direct liposome-mediated gene transfer in vivo is also described. This method uses a pump system or automatic system to continually apply liposome/DNA complexes at timed intervals.
IT Liposome
(DOPE/DAC-Chol liposome; cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)
IT Apparatus
Genetic engineering
Pumps
Transformation, genetic
(cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Antibodies
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Deoxyribonucleic acids
RL: BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Gene, animal
RL: BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Virus, animal
(fusion proteins; cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Phosphoproteins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HMG1, cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Proteins, specific or class
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(core, cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Proteins, specific or class
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fusion products, viral; cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT Therapeutics
(geno-, cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT 2462-63-7
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DOPE/DAC-Chol liposome; cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

Searcher : Shears 308-4994

IT 137056-72-5P
RL: BUU (Biological use, unclassified); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT 110-70-3, N,N'-Dimethylethylenediamine
RL: RCT (Reactant)
(reaction with chloroformate cholesterol; cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT 7144-08-3, Cholesterol, chloroformate
RL: RCT (Reactant)
(reaction with dimethylethylenediamine; cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

IT 67-56-1, Methanol, uses 67-66-3, Trichloromethane, uses 7631-86-9, Silica, uses
RL: NUU (Nonbiological use, unclassified); USES (Uses)
(silica gel and tricholormethane/methanol for purifn.; cholesterol (dimethylaminoethane)carbamoyl deriv. prepn. and use for liposome-mediated gene transfer)

L6 ANSWER 12 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 11
AN 126:44183 CA
TI DNA-Induced Lateral Segregation of Cationic Amphiphiles in Lipid Bilayer Membranes as Detected via 2H NMR
AU Mitrakos, Peter; Macdonald, Peter M.
CS Department of Chemistry, University of Toronto, Mississauga, ON, L5L 1C6, Can.
SO Biochemistry (1996), 35(51), 16714-16722
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
OS CJACS-IMAGE; CJACS
AB 2H NMR spectroscopy was used to investigate the response of specifically choline-deuterated 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) to changes in surface electrostatic charge in membranes consisting of mixts. of POPC plus various cationic amphiphiles plus polyadenylic acid (Polys). Three different cationic amphiphiles were investigated: cetyltrimethylammonium bromide (CTAB), dioleoyldimethylaminopropane (DODAP), and 3 .**beta**.[N-(N',N'-dimethylaminoethane)**carbamoyl**] **cholesterol** (DC-CHOL). Each of the cationic amphiphiles elicited a concn.-dependent decrease (increase) in the quadrupolar splitting from POPC-.alpha.-d2 (POPC-.beta.-d2), as expected for the accumulation of cationic charges at the surface of a lipid bilayer. However, the strength of the response varied with the cationic

amphiphile in the order CTAB > DODAP > DC-CHOL. When polyA was added to the cationic amphiphile-contg. lipid bilayers, the 2H NMR spectrum consisted of two overlapping Pake patterns, indicating the presence of two lipid domains with different effective surface charges and only slow exchange of lipids between the two domains. There was no evidence of any non-bilayer lipid arrangements. Anal. of the quadrupolar splittings of the two 2H NMR spectral components demonstrated that the polyA-contg. domain was enriched with respect to cationic amphiphiles while the polyA-free domain was depleted with respect to cationic amphiphiles. We conclude that polyA is able to laterally segregate cationic amphiphiles into long-lived lipid domains of distinct compn.

IT Amphiphiles
Bilayer (biological membrane)
(DNA-induced lateral segregation of cationic amphiphiles in lipid bilayer membranes as detected via 2H NMR)

IT 24937-83-5, Poly(A)
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(DNA-induced lateral segregation of cationic amphiphiles in lipid bilayer membranes as detected via 2H NMR)

IT 57-09-0, Cetyltrimethylammonium bromide 127512-29-2 137056-72-5
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(DNA-induced lateral segregation of cationic amphiphiles in lipid bilayer membranes as detected via 2H NMR)

L6 ANSWER 13 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 12
AN 124:252118 CA
TI Folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer
AU Lee, Robert J.; Huang, Leaf
CS Lab. Drug Targeting, Dep. Pharm., Univ. Pittsburgh Sch. Med., Pittsburgh, PA, 15261, USA
SO J. Biol. Chem. (1996), 271(14), 8481-7
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB We have developed a lipidic gene transfer vector, LPDII, where DNA was first complexed to polylysine at a ratio of 1:0.75 (wt./wt.) and then entrapped into folate-targeted pH-sensitive anionic liposomes composed of dioleoyl phosphatidylethanolamine (DOPE)/cholesteryl hemisuccinate/folate-polyethylene glycol-DOPE (6:4:0.01 mol/mol) via charge interaction. LPDII transfection of KB cells, a cell line overexpressing the tumor marker folate receptor, was affected by both the lipid to DNA ratio and the lipid compn. At low lipid to DNA ratios (e.g. 4 and 6), LPDII particles were pos. charged; transfection and cellular uptake levels were independent of the folate receptor and did not require a pH-sensitive lipid compn.

Meanwhile, transfection and uptake of neg. charged LPDII particles, i.e. those with high lipid to DNA ratios (e.g. 10 and 12), were folate receptor-dependent and required a pH-sensitive lipid compn. The transfection activity of LPDII was lost when the inverted cone-shaped DOPE was replaced by dioleoyl phosphatidylcholine. LPDII particles with lipid to DNA ratios of 4, 6, 10, and 12 were .apprx.20-30 times more active than DNA.cntdot.3-. **beta**.-[N-(N',N'-dimethylethane)**carbamoyl**] **cholesterol** cationic liposome complexes in KB cells and were much less cytotoxic. On the sucrose gradient, LPDII particles had a migration rate in between those of the free DNA and the DNA.cntdot.polylysine complex. An electron micrograph of LPDII showed a structure of spherical particles with a pos. stained core enclosed in a lipidic envelope with a mean diam. of 74 .+-. 14 nm. This novel gene transfer vector may potentially be useful in gene therapy for tumor-specific delivery.

IT Liposome
(anionic; folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer)

IT Neoplasm
(cell; folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer)

IT Transformation, genetic
(folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer)

IT Deoxyribonucleic acids
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(lipidic gene transfer vector LPDII transfection of KB cells, a cell line overexpressing the tumor marker folate receptor, was affected by both the lipid to DNA ratio and the lipid compn.)

IT pH
(tumor cell transfection and uptake of neg. charged LPDII particles, i.e. those with high lipid to DNA ratios (e.g. 10 and 12), were folate receptor-dependent and required a pH-sensitive lipid compn.)

IT Animal cell line
(KB, lipidic gene transfer vector LPDII transfection of KB cells, a cell line overexpressing the tumor marker folate receptor, was affected by both the lipid to DNA ratio and the lipid compn.)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(folic acid, tumor cell transfection and uptake of neg. charged

LPDII particles, i.e. those with high lipid to DNA ratios (e.g. 10 and 12), were folate receptor-dependent and required a pH-sensitive lipid compn.)

IT 1510-21-0, Cholesteryl hemisuccinate 2462-63-7, Dioleoyl phosphatidylethanolamine 25322-68-3, Polyethylene glycol
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(anionic liposomes composed of dioleoyl phosphatidylethanolamine (DOPE)/cholesteryl hemisuccinate/folate-polyethylene glycol-DOPE (6:4:0.01 mol/mol) for tumor cell-specific gene transfer)

IT 25104-18-1, Polylysine
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer)

IT 59-30-3, Folic acid, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer)

L6 ANSWER 14 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 13
AN 126:162137 CA
TI New cationic lipid formulations for gene transfer
AU Liu, Feng; Yang, Jingping; Huang, Leaf; Liu, Dexi
CS Dep. Pharmaceutical Sciences, SchoolPharmacy, Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SO Pharm. Res. (1996), 13(12), 1856-1860
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum
DT Journal
LA English
AB An attempt was made to develop dosage forms of DNA for gene delivery. **3.beta.**[N-(N',N' imethylaminoethane) **carbamoyl]cholesterol** (DC-Chol) was mixed either with Tween 80 alone, or with addnl. lipid components including castor oil and phosphatidylcholine (PC) or dioleoyphosphatidylethanolamine (DOPE) to make different lipid formulations. The particle size and the phys. stability of the formulations upon mixing with plasmid DNA contg. the luciferase cDNA were examd. using laser light scattering measurement. The transfection activity of the DNA/lipid complexes was tested in presence or absence of serum using a cell culture system. Many favorable properties as a gene carrier could be achieved by formulating DNA into new dosage forms using Tween 80 as the major emulsifier. Compared to the cationic liposomes, these new formulations transfected different cell lines with an equiv. or higher efficiency. Not only are they resistant to serum, but also form stable DNA complexes which could be stored for longer periods

of time without losing transfection activity. Cationic lipids formulated into different lipid formulations using Tween 80 as a surfactant appeared to have more favorable phys. and biol. activities than traditional cationic liposomes as a carrier for gene delivery.

IT Gene therapy
Liposomes (drug delivery systems)
Particle size
Serum (blood)
Transformation (genetic)
(cationic lipid formulations for gene transfer)

IT Castor oil
DNA
Lipids, biological studies
Phosphatidylcholines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic lipid formulations for gene transfer)

IT 2462-63-7, Dioleoylphosphatidylethanolamine 9005-65-6, Tween 80
137056-72-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic lipid formulations for gene transfer)

L6 ANSWER 15 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 14
AN 126:108822 CA
TI Effect of non-ionic surfactants on the formation of DNA/Emulsion complexes and emulsion-mediated gene transfer
AU Liu, Feng; Yang, Jingping; Huang, Leaf; Liu, Dexi
CS School of Pharmacy, Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SO Pharm. Res. (1996), 13(11), 1642-1646
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum
DT Journal
LA English
AB The structure-function relationship of non-ionic surfactants in emulsion-mediated gene delivery is studied. Four different types of non-ionic surfactants including Tween, Span, Brij and pluronic copolymers were used as co-emulsifiers for prepn. of emulsions composed of castor oil, dioleoylphosphatidylethanolamine (DOPE) and **3.beta.**[N-(N',N'-dimethylaminoethane) **carbamoyl**] **cholesterol** (DC-Chol). The effect of different surfactants on the formation of DNA/emulsion complexes and transfection activity were analyzed using plasmid DNA contg. luciferase cDNA as a reporter gene. Non-ionic surfactants contg. branched polyoxyethylene chains as the hydrophilic head group were more effective in preventing the formation of large DNA/emulsion complexes than those contg. one or no polyoxyethylene chain. All emulsion formulations except those contg. Brij 700 exhibited high activity in transfecting mouse BL-6 cells in the absence of serum. In the presence of serum, however, transfection activity of each

formulation varied significantly. Emulsions contg. Tween Brij 72, pluronic F68 and F127 demonstrated increased activity in transfecting cells in the presence of 20% serum. In contrast to emulsions contg. Span, long chain polyoxyethylene of Brji showed decreased transfection activity. The particle size of the DNA/emulsion complexes and their ability to transfect cells are dependent on the concn. of non-ionic surfactant in the formulation. Conclusions. The structure of the hydrophilic head group of the nonionic surfactants in the emulsion is important in detg. how DNA mols. interact with emulsions and the extent to which DNA is transferred inside the cell.

IT Emulsifying agents
Emulsions (drug delivery systems)
Nonionic surfactants
Particle size
Transformation (genetic)
(effect of non-ionic surfactants on formation of DNA/emulsion complexes and emulsion-mediated gene transfer)

IT Castor oil
DNA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of non-ionic surfactants on formation of DNA/emulsion complexes and emulsion-mediated gene transfer)

IT 1338-39-2, Span 20 1338-41-6, Span 60 1338-43-8, Span 80 2462-63-7, Dioleoylphosphatidylethanolamine 9005-00-9, Brij 72 9005-64-5, Tween 20 9005-65-6, Tween 80 9005-66-7, Tween 40 9005-67-8, Tween 60 26266-57-9, Span 40 106392-12-5, Pluronic f68 137056-72-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of non-ionic surfactants on formation of DNA/emulsion complexes and emulsion-mediated gene transfer)

L6 ANSWER 16 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 15
AN 126:69795 CA
TI The use of cationic liposomes DC-CHOL/DOPE and DDAB/DOPE for direct transfer of Escherichia coli cytosine deaminase gene into growing melanoma tumors
AU Szala, S.; Missol, E.; Sochanik, A.; Strozyk, M.
CS Dep. Tumor Biol., Inst. Oncol., Gliwice, 44-100, Pol.
SO Gene Ther. (1996), 3(11), 1026-1031
CODEN: GETHEC; ISSN: 0969-7128
PB Stockton
DT Journal
LA English
AB An attempt was made to use simple cationic liposomes DC-Chol/DOPE and DDAB/DOPE (DC-Chol is **3.beta**
.-(N(N',N'-dimethylaminoethane) **carbamoyl**)
cholesterol, DDAB is dimethyldioctadecyl ammonium bromide and DOPE is dioleoylphosphatidylethanolamine) for transfer of

Escherichia coli cytosine deaminase 'suicide' gene under the control of tissue-specific tyrosinase gene promoter directly into the murine melanoma B16(F10) tumor. Several repeated intratumoral injections of DNA-liposome complexes followed by i.p. administrations of 5-fluorocytosine, which is converted to 5-fluorouracil, caused strong retardation of murine melanoma B16(F10) tumor growth and, in some cases, rejection of the pre-established tumor. The inhibition of tumor growth expressed as the increased survival of mice is better seen in the case of using DNA-DDAB/DOPE complexes as compared to DNA-DC-Chol/DOPE ones. It seems that the obsd. therapeutic effect appears to result from several factors; 5-fluorouracil generation by transfected cells, liposome toxicity (DDAB is more toxic than DC-Chol and hence more tumor cells are killed), increased transfection efficiency of surviving cancer cells (in this case DDAB is a better transfection agent than DC-Chol) and, finally, the bystander effect which causes destruction of cells untransfected with CD gene by easily diffusible 5-fluorouracil.

IT Escherichia coli
Gene therapy
Liposomes (drug delivery systems)
Melanoma inhibitors
(the use of cationic liposomes DC-CHOL/DOPE and DDAB/DOPE for direct transfer of Escherichia coli cytosine deaminase gene into growing melanoma tumors)

IT Genes (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(the use of cationic liposomes DC-CHOL/DOPE and DDAB/DOPE for direct transfer of Escherichia coli cytosine deaminase gene into growing melanoma tumors)

IT 9002-10-2, Tyrosinase 9025-05-2, Cytosine deaminase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(the use of cationic liposomes DC-CHOL/DOPE and DDAB/DOPE for direct transfer of Escherichia coli cytosine deaminase gene into growing melanoma tumors)

IT 51-21-8, 5-Fluorouracil 2022-85-7, 5-Fluorocytosine 2462-63-7, Dioleoylphosphatidylethanolamine 3700-67-2, Dimethyldioctadecyl ammonium bromide 137056-72-5
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(the use of cationic liposomes DC-CHOL/DOPE and DDAB/DOPE for direct transfer of Escherichia coli cytosine deaminase gene into growing melanoma tumors)

L6 ANSWER 17 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 16
AN 125:95723 CA
TI Fate of cationic liposomes and their complex with oligonucleotide in vivo

AU Litzinger, David C.; Brown, Jeffrey M.; Wala, Iwona; Kaufman, Stephen A.; Van, Gwyneth Y.; Farrell, Catherine L.; Collins, David
CS Department of Pharmacology, Amgen, Inc., Thousand Oaks, CA, 91320, USA
SO Biochim. Biophys. Acta (1996), 1281(2), 139-149
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB The present studies describe the biodistribution of cationic liposomes and cationic liposome/oligonucleotide complex following i.v. injection into mice via the tail vein. 111In-diethylenetriaminepentaacetic acid stearylamide (111In-DTPA-SA) was used as a lipid-phase radiolabel. Inclusion of up to 5 mol DTPA-SA in liposomes composed of **3.beta.-(N-(N',N'-dimethylaminoethane)carbamoyl)cholesterol** (DC-Chol) and dioleoylphosphatidylethanolamine (DOPE) did not influence liposome formation or size, nor the binding/uptake or fusion of the cationic liposomes with CHO cells in vitro. Moreover, nuclear delivery of oligonucleotide to CHO cells was unaffected by the probe. The biodistribution of liposomes with increasing concn. of DC-Chol (1:4-4:1, DC-Chol/DOPE, mol/mol) at 24 h post-injection revealed no dependence on lipid compn. Uptake was primarily by liver, and accumulation in spleen and skin was also obsd. Comparatively little accumulation occurred in lung. Clearance of injected liposomes by liver was very rapid (.apprx.84.5 of the injected dose by 7.5 h post-injection). Liposome uptake by liver and spleen were equally efficient in the dose range of 3.33 to 33.33 mg/kg body wt., yet possible satn. of liver uptake at a dose of 66.80 mg/kg may have allowed for increased spleen accumulation. Preincubation of cationic liposomes with phosphorothioate oligonucleotide induced a dramatic yet transient accumulation of the lipid in lung which gradually redistributed to liver. Similar results were obsd. when monitoring iodinated oligonucleotide in the complex. Immuno-histochem. studies revealed large aggregates of oligonucleotide within pulmonary capillaries at 15 min post-injection, suggesting the early accumulation in lung was due to embolism. Immuno-histochem. studies further revealed labeled oligonucleotide to be localized primarily to Kupffer cells at 24 h post-injection. Immuno-electron microscopy revealed localization of oligonucleotide primarily to the lumen of pulmonary capillaries at 15 min post-injection, and to phagocytic vacuoles of Kupffer cells at 24 h post-injection. By these methods, nuclear delivery of oligonucleotide in vivo was not obsd. Increasing concn. of mouse serum inhibited cellular binding/uptake of cationic liposomes in vitro, without or with complexed oligonucleotide. We therefore postulate that interaction with plasma components, including opsonin(s), inhibits cellular uptake of the injected liposomes as well as the liposome/oligonucleotide complex, and mediates rapid uptake by Kupffer cells of the liver. These results are relevant to

the design of cationic liposomes for efficient delivery of nucleic acid in vivo.

IT Nucleic acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(delivery of; pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

IT Lung
Spleen
(pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

IT Opsonins
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

IT Liver
(Kupffer cell, pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

IT Pharmaceutical dosage forms
(liposomes, cationic; pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

IT Nucleotides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligo-, pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

IT Nucleotides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligo-, deoxyribo-, thiophosphate-linked, pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

IT 2462-63-7, Dioleoylphosphatidylethanolamine 137056-72-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of cationic liposomes for delivery of antisense oligonucleotides)

L6 ANSWER 18 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 17
AN 126:122406 CA
TI Large scale production of DC-Chol cationic liposomes by microfluidization
AU Sorgi, Frank L.; Huang, Leaf
CS Departments of Pharmaceutical Sciences and Pharmacology, The Laboratory of Drug Targeting, The University of Pittsburgh, Pittsburgh, PA, 15261, USA
SO Int. J. Pharm. (1996), 144(2), 131-139
CODEN: IJPHDE; ISSN: 0378-5173
PB Elsevier
DT Journal
LA English
AB In this report, we describe the large scale prodn. and testing of DC-Chol [3.**beta**.-[N-(N,N-dimethylaminoethyl)

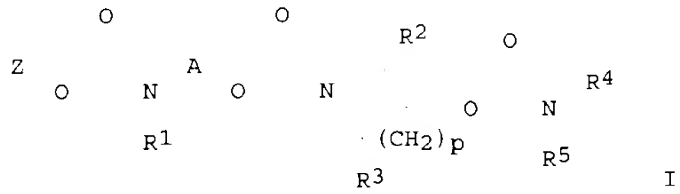
carbamoyl]cholesterol] cationic liposomes by microfluidization. These liposomes are produced in a good manufg. practice acceptable manner to a 500 mL batch size and are shown to be sterile. Further, when stored at 4.degree.C, DC-Chol liposomes will retain their original size, remain suspended in soln., and retain activity for a period exceeding 1.5 yr. In-process quality assurance and quality control procedures have identified problems in processing and methods to produce a final product of pharmaceutical quality have been developed to overcome these obstacles. Assays for product content (DC-Chol and DOPE assays), size, sterility, endotoxin detn., storage conditions and shelf life have been developed. Successful lots have been used in a human gene therapy clin. trial for cystic fibrosis at Oxford University as well as many pre-clin. expts. throughout the world. Implications for application to further gene therapy clin. trials as well as the development of liposome vector programs are discussed in detail.

IT Liposomes (drug delivery systems)
(large scale prodn. of DC-Chol cationic liposomes by microfluidization)

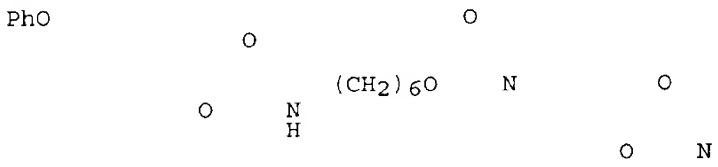
IT Fluidization
(microfluidization; large scale prodn. of DC-Chol cationic liposomes by microfluidization)

IT 4004-05-1, Dioleoylphosphatidylethanolamine 144108-30-5
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(large scale prodn. of DC-Chol cationic liposomes by microfluidization)

L6 ANSWER 19 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 18
AN 124:260850 CA
TI 4-(Carbamoyloxy)piperidine-1-carboxylic acid esters as inhibitors of cholesterol absorption
IN LaClair, Christa Marie; Laclair, Christa Marie
PA American Home Products Corp., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
PI WO 9534539 A1 951221
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, UZ
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US4938 950418
PRAI US 94-259229 940613
DT Patent
LA English
OS MARPAT 124:260850
GI



I



II

AB The title compds. inhibit the enzyme cholesterol ester hydrolase (CEH), and thus inhibit the formation of esterified cholesterol. Since esterified cholesterol is absorbed through the intestine, inhibition of the enzyme results in inhibition of cholesterol absorption. The compds. have formula I [wherein p= 0-4; Z = -Ar1, -Ar1Ar2, -Ar1OAr2, -Ar1SAr2, -Ar1OCOAr2, -Ar1COOAr2, -Ar1COAr2, -Ar1(CH2)1-20Ar2, -Ar1(CH2)1-20OAr2, -Ar1O(CH2)1-20Ar2, -Ar1(CR6:CR6)1-3Ar2, or -Ar1NR7Ar2; Ar1, Ar2 = various arom. and heteroarom ring systems; A = hydrocarbon linking group which may be interrupted by heteroatom or cycloalkyl, aryl, heterocycloalkyl, or azacycloalkyl; R1 = H, alkyl, (un)substituted Ph; or AR1 forms heterocyclic ring; R2, R3 = alkyl, alkoxy, alkylcarbonyl, OH, cyano, etc.; R4, R5 = H, alkyl, alkenyl, acyl, alkoxycarbonyl, etc.; or NR4R5 = satd. heterocyclic ring; R6 = H, alkyl; R7 = H, alkyl, alkanoyl, alkoxycarbonyl]. For example, 4-phenoxyphenol was converted to its 4-nitrophenyl carbonate ester (73%), which was amidated with 6-amino-1-hexanol (70%). The obtained alc. carbamate was again converted to a 4-nitrophenyl carbonate ester (61%), which was again amidated, this time with 4-hydroxypiperidine (71%). Repeating the same cycle with the product and six different amines gave six title compds., e.g. (using piperidine), II. At 10 mg/kg orally in normal rats, II gave an 81% decrease in absorption of radiolabeled cholesterol.

IT Intestine
(absorption through; prepn. of (carbamoyloxy)piperidinecarboxylate esters as cholesterol absorption inhibitors)

IT Anticholesteremics and Hypolipemics
(prepn. of (carbamoyloxy)piperidinecarboxylate esters as cholesterol absorption inhibitors)

IT Antiarteriosclerotics
(antiatherosclerotics, prepn. of (carbamoyloxy)piperidinecarboxyl ate esters as cholesterol absorption inhibitors)

IT 112-80-1, Oleic acid, reactions
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study)
(esterification; prepn. of (carbamoyloxy)piperidinecarboxylate esters as cholesterol absorption inhibitors)

IT 303-43-5P, Cholesteryl oleate
RL: PNU (Preparation, unclassified); PREP (Preparation)
(inhibition of formation; prepn. of (carbamoyloxy)piperidinecarbo xylate esters as cholesterol absorption inhibitors)

IT 9026-00-0, Cholesteryl ester hydrolase
RL: BPR (Biological process); CAT (Catalyst use); BIOL (Biological study); PROC (Process); USES (Uses)
(inhibition; prepn. of (carbamoyloxy)piperidinecarboxylate esters as cholesterol absorption inhibitors)

IT 162321-08-6P, Carbonic acid 4-nitrophenyl 4-phenoxyphenyl ester
174960-44-2P, (6-Hydroxyhexyl)carbamic acid 4-phenoxyphenyl ester
174960-45-3P 174960-46-4P 174960-47-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(intermediate; prepn. of (carbamoyloxy)piperidinecarboxylate esters as cholesterol absorption inhibitors)

IT 174960-38-4P 174960-39-5P 174960-40-8P 174960-41-9P
174960-42-0P 174960-43-1P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (carbamoyloxy)piperidinecarboxylate esters as cholesterol absorption inhibitors)

IT 57-88-5, Cholest-5-en-3-ol (**3.beta.**)-, reactions
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study)
(prepn. of (**carbamoyloxy**)piperidinecarboxylate esters as **cholesterol** absorption inhibitors)

IT 108-91-8, Cyclohexylamine, reactions 110-89-4, Piperidine, reactions 111-26-2, 1-Hexanamine 831-82-3, 4-Phenoxyphenol 1123-30-4, 8-Azaspiro[4.5]decane hydrochloride 2016-57-1, Decylamine 4048-33-3, 6-Amino-1-hexanol 5382-16-1, 4-Hydroxypiperidine 7693-46-1, 4-Nitrophenyl chloroformate 13214-66-9, 4-Phenylbutylamine
RL: RCT (Reactant)
(starting material; prepn. of (carbamoyloxy)piperidinecarboxylate esters as cholesterol absorption inhibitors)

L6 ANSWER 20 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 19
AN 123:6532 CA
TI Fusion of cationic liposomes with mammalian cells occurs after endocytosis

AU Wrobel, Iwona; Collins, David
CS Department of Pharmaceutics and Drug Delivery, Mail stop 8-1-A-215, Amgen, Inc., 1840 DeHavilland Drive, Thousand Oaks, CA, 91320, USA
SO Biochim. Biophys. Acta (1995), 1235(2), 296-304
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB The interaction of cationic liposomes prepd. using either dioleoyltrimethylammonium propane (DOTAP) or 3.**beta**.-(N-(N',N'-dimethylaminoethane)**carbamoyl**)**cholesterol** (DC-CHOL) with model membranes and with cultured mammalian cells was examd. using an assay developed for monitoring virus-cell fusion (Stegmann et al. (1993) Biochem. 32, 11330-11337). Lipid mixing between cationic liposomes and liposomes composed of DOPE/dioleoylphosphatidylglycerol (DOPG) or dioleoylphosphatidylcholine (DOPC)/DOPG was insensitive to pH in the range of pH 4.5-7.0 and was not affected by sodium chloride concn. in the range of 0-150 mM. Lipid mixing was dependent on dioleoylphosphatidylethanolamine (DOPE), since cationic liposomes prepd. using dioleoylphosphatidylcholine (DOPC) were incapable of lipid mixing with DOPC/DOPG liposomes. The interaction of cationic liposomes with Hep G-2 and CHO D- cells was also studied. For both cell types, liposome-cell lipid mixing was rapid at 37.degree.C, beginning within minutes and continuing for up to 1 h after uptake. The extent of lipid mixing was decreased at 15.degree.C, esp. at later (.gtoreq.20 min) time points. This suggests that at least part of the obsd. lipid mixing occurred after reaching cellular lysosomes. No lipid mixing was seen at 4.degree.C. Monensin inhibited lipid mixing between cationic liposomes and the cells, despite having no effect on liposome uptake. Inhibition of endocytic uptake of liposomes, either by incubation in hypertonic media or by depletion of cellular ATP with sodium azide and 2-deoxyglucose abolished liposome-cell fusion in both cell types. These data demonstrate that binding to the cell surface is insufficient for cationic liposome-cell fusion and that uptake into the endocytic pathway is required for fusion to occur.
IT Liposome
(cationic; fusion of cationic liposomes with mammalian cells occurs after endocytosis)
IT Animal cell
Fusion, biological
(fusion of cationic liposomes with mammalian cells occurs after endocytosis)
IT Biological transport
(endocytosis, fusion of cationic liposomes with mammalian cells occurs after endocytosis)
IT 2462-63-7, Dioleoylphosphatidylethanolamine 62700-69-0, Dioleoylphosphatidylglycerol 113669-21-9, DOTAP 137056-72-5
RL: BPR (Biological process); BIOL (Biological study); PROC

(Process)
(fusion of cationic liposomes with mammalian cells occurs after endocytosis)

L6 ANSWER 21 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 20
AN 122:307619 CA
TI The role of dioleoyl phosphatidylethanolamine in cationic liposome mediated gene transfer
AU Farhood, Hassan; Serbina, Natalya; Huang, Leaf
CS Department of Pharmacology, University of Pittsburgh School of Medicine, 13th Floor, Biomedical Science Tower, Pittsburgh, PA, 15261, USA
SO Biochim. Biophys. Acta (1995), 1235(2), 289-95
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB In a reporter gene assay, cationic liposomes contg. the cationic lipid **3.beta.-(N-(N',N'-dimethylaminoethane) carbamoyl)cholesterol** (DC-Chol) and a neutral phospholipid dioleoylphosphatidylethanolamine (DOPE) showed high transfection activity. DNA/liposome complex which contained low amt. of liposomes could bind to the cell surface but failed to transfect the cells. We have designed a two-step protocol to examine this phenomenon in more detail. A431 human cells were incubated on ice (pulse) with DNA complexed to a low level of cationic liposomes. The cells were washed and incubated at 37.degree.C (chase) with or without free cationic liposomes of various compn. (helper liposomes). Only liposomes enriched with DOPE showed helper activity; liposomes contg. dioleoylphosphatidylcholine (DOPC), a structural analog of DOPE, had no helper activity. The delivery was inhibited by the lysosomotropic agent chloroquine and was optimal if the helper liposome chase was initiated immediately after the pulse. An endocytosis model of DNA delivery by cationic liposomes is proposed in which the principal function of the chase liposomes is to destabilize the endosome membrane and allow the release of DNA into the cytosol. This model is consistent with the known activity of DOPE to assume non-bilayer structures, hence destabilizing the endosome membrane.
IT Deoxyribonucleic acids
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(A431 human cells were incubated on ice (pulse) with DNA complexed to a low level of cationic liposomes, and only liposomes enriched with dioleoylphosphatidylethanolamine showed helper activity for genetic transformation)
IT Cell membrane
(an endocytosis model of DNA delivery by cationic liposomes is proposed in which the principal function of the chase liposomes

is to destabilize the endosome membrane and allow the release of DNA into the cytosol)

IT Liposome
Transformation, genetic
(role of dioleoylphosphatidylethanolamine in cationic liposome mediated gene transfer)

IT Animal cell line
(A431, role of dioleoylphosphatidylethanolamine in cationic liposome mediated gene transfer in human A431 cells)

IT Biological transport
(endocytosis, an endocytosis model of DNA delivery by cationic liposomes is proposed in which the principal function of the chase liposomes is to destabilize the endosome membrane and allow the release of DNA into the cytosol)

IT 54-05-7, Chloroquine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(an endocytosis model of DNA delivery by cationic liposomes is proposed in which the principal function of the chase liposomes is to destabilize the endosome membrane and allow the release of DNA into the cytosol)

IT 137056-72-5
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cationic liposomes contg. the cationic lipid **3** **.beta.**-(N-(N',N'-dimethylaminoethane)**carbamoyl**) **cholesterol** (DC-Chol) and a neutral phospholipid dioleoylphosphatidylethanolamine (DOPE) showed high transfection activity)

IT 2462-63-7, Dioleoylphosphatidylethanolamine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(role of dioleoylphosphatidylethanolamine in cationic liposome mediated gene transfer)

L6 ANSWER 22 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 21
AN 121:28017 CA
TI A sustained, cytoplasmic transgene expression system delivered by cationic liposomes
AU Gao, Xiang; Jaffurs, Daniel; Robbins, Paul D.; Huang, Leaf
CS Sch. Med., Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SO Biochem. Biophys. Res. Commun. (1994), 200(3), 1201-6
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB A plasmid contg. the reporter gene, chloramphenicol acetyltransferase (CAT), driven by the bacteriophage T7 promoter was co-delivered with purified T7 RNA polymerase by the **3**. **beta**.[N-(N',N'-dimethylaminoethane)-**carbamoyl**] **cholesterol** cationic liposomes into human embryonic kidney

293 cells to obtain a transient (2 days) CAT gene expression. To prolong the expression, a T7 autogene which contains the T7 RNA polymerase gene driven by the T7 promoter was included in the transfection complex as a self-amplifying regeneration mechanism for the polymerase. High level CAT gene expression was obsd. up to 5 days after transfection. This strong and sustained expression system should be useful in gene transfer expts.

IT Plasmid and Episome
(bacteriophage T7 promoter and RNA polymerase gene in, for cationic liposome delivery to human cell, in gene expression system)

IT Transformation, genetic
(cationic liposome delivery of plasmid contg. bacteriophage T7 RNA polymerase and other gene in, of human cell, as gene expression system)

IT Liposome
(dimethylaminoethane-carbamoyl cholesterol, plasmid contg. bacteriophage T7 promoter and RNA polymerase gene delivery by, for gene expression in transfected human cell)

IT Gene
RL: BIOL (Biological study)
(expression of, in transfected human cell, plasmid contg. bacteriophage T7 promoter and RNA polymerase gene delivered by cationic liposome for)

IT Gene, microbial
RL: BIOL (Biological study)
(for RNA polymerase, in plasmid, cationic liposome for delivery of, in gene expression in transfected human cell)

IT Animal cell
(transfection of human, as gene expression system, cationic liposome delivery of plasmid contg. bacteriophage T7 RNA polymerase and other gene in)

IT Virus, bacterial
(T7, promoter of, gene for RNA polymerase and other gene regulation by, in human cell transfected by plasmid delivered by cationic liposome)

IT Genetic element
RL: BIOL (Biological study)
(promoter, gene for RNA polymerase and other gene regulation by, of bacteriophage T7, in human cell transfected by plasmid delivered by cationic liposome)

IT 137056-72-5
RL: USES (Uses)
(liposome, plasmid contg. bacteriophage T7 promoter and RNA polymerase gene delivery by, for gene expression in transfected human cell)

IT 9014-24-8, RNA polymerase
RL: USES (Uses)
(plasmid contg. bacteriophage T7 promoter and gene for, cationic

liposome for delivery of, in gene expression in transfected human cell)

L6 ANSWER 23 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 22
AN 121:42651 CA
TI Direct gene transfer by liposomes
AU Singhal, Arun; Huang, Leaf
CS Dep. Pharmacol., Univ. Pittsburgh, PA, 15261, USA
SO J. Liposome Res. (1994), 4(1), 289-99
CODEN: JLREE7; ISSN: 0898-2104
DT Journal
LA English
AB Cationic liposomes are widely used for the delivery of genes both in vivo and in clin. trials. Thus, a **3.beta**.-[N-(N',N'-dimethylaminoethyl)**carbamoyl**] **cholesterol** (DC-chol) liposome formulation was developed by the authors for relatively high activity of transfection and low level of toxicity for most cell types. Different strategies are described for achieving regulated transgene expression as well as expression for a prolonged period of time using DC-chol liposomes.
IT Gene, animal
RL: PRP (Properties)
(transfer of, by cationic liposomes)
IT Pharmaceutical dosage forms
(liposomes, cationic, direct gene transfer by)
IT 137056-72-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical liposomes contg., direct gene transfer by)

L6 ANSWER 24 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 23
AN 123:47107 CA
TI DC-chol liposomes as DNA carriers for gene therapy
AU Singhal, Arun; Huang, Leaf
CS Department Pharmacology, University Pittsburgh School Medicine, Pittsburgh, PA, 15261, USA
SO Gene Ther. (1994), 107-29. Editor(s): Hui, Kam Man. Publisher: World Sci., Singapore, Singapore.
CODEN: 61JCAW
DT Conference; General Review
LA English
AB A review, with 38 refs., discussing the authors' work with various liposomes as DNA carriers for gene therapy. In particular, liposomes contg. DC-chol (**3.beta**.[N-(N',N-dimethylaminoethane)**carbamoyl**] **cholesterol**) have shown versatility in administering DNA-liposome complexes in vivo and have been proven to be a safe reagent in clin. uses.. The liposomes can be manufd. in large quantities with pharmaceutical quality.
IT Deoxyribonucleic acids

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(liposomes contg. [(dimethylaminoethane)carbamoyl]cholesterol as DNA carriers for gene therapy)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(liposomes contg. [(dimethylaminoethane)carbamoyl]cholesterol as DNA carriers for gene therapy)

IT Therapeutics
(geno-, liposomes contg. [(dimethylaminoethane)carbamoyl]cholesterol as DNA carriers for gene therapy)

IT Pharmaceutical dosage forms
(liposomes, liposomes contg. [(dimethylaminoethane)carbamoyl]cholesterol as DNA carriers for gene therapy)

IT 137056-72-5
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liposomes contg. [(dimethylaminoethane)carbamoyl]cholesterol as DNA carriers for gene therapy)

L6 ANSWER 25 OF 25 CA COPYRIGHT 1997 ACS DUPLICATE 24
AN 115:225390 CA
TI A novel cationic liposome reagent for efficient transfection of mammalian cells
AU Gao, Xiang; Huang, Leaf
CS Dep. Biochem., Univ. Tennessee, Knoxville, TN, 37996-0840, USA
SO Biochem. Biophys. Res. Commun. (1991), 179(1), 280-5
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB A novel cationic deriv. of **cholesterol**, 3. **beta**.[N-(N',N'-dimethylaminoethane)-**carbamoyl**] **cholesterol** (DC-Chol), has been synthesized and used to prep. sonicated liposomes with dioleoylphosphatidylethanolamine. This novel cationic liposome reagent facilitates efficient DNA mediated transfection in A431 human epidermoid carcinoma cells, A549 human lung carcinoma cells, L929 mouse fibroblast cells, and YPT minipig primary endothelial cells. The activity was greater than that of a com. reagent, Lipofectin, and was approx. 4-fold less toxic than Lipofectin when assayed with A431 cells. The reagent is easy to synthesize and stable for at least 6 wk.

IT Liposome
(cationic, DC-cholesterol reagent for, for efficient transfection of mammalian cells)

IT Transformation, genetic
(using cationic liposomes, DC-cholesterol reagent for)

IT 2462-63-7, Dioleoylphosphatidylethanolamine
RL: PRP (Properties)
(as cationic liposome reagent with DC-cholesterol, for efficient

transfection of mammalian cells)
IT 137056-72-5P
RL: PREP (Preparation)
(prepn. of, as cationic liposome reagent for efficient transfection of mammalian cells)
IT 108-00-9 7144-08-3, Cholesteryl chloroformate
RL: RCT (Reactant)
(reaction of, in prepn. of DC-cholesterol)

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(FILE 'BIOSIS, MEDLINE, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, DISSABS, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB, DRUGLAUNCH' ENTERED AT 16:17:32 ON 15 DEC 1997)
L7 4572 S L4
L8 87 S L7(S)(CARBAM? OR CARBOXAMID? OR CARBOX? AMID?)

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PROCESSING COMPLETED FOR L8
L9 39 DUP REM L8 (48 DUPLICATES REMOVED)

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L9 ANSWER 1 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS
AN 97:347639 BIOSIS
DN 99646842
TI Intratumoral pharmacokinetics and in vivo gene expression of naked plasmid DNA and its cationic liposome complexes after direct gene transfer.
AU Nomura T; Nakajima S; Kawabata K; Yamashita F; Takakura Y; Hashida M
CS Dep. Drug Delivery Res., Fac. Pharmaceutical Sci., Kyoto Univ., Sakyo-ku, Kyoto 606-01, Japan
SO Cancer Research 57 (13). 1997. 2686-2686. ISSN: 0008-5472
LA English
AB The pharmacokinetic properties and gene expression of naked plasmid DNA and its cationic liposome complexes were studied after direct intratumoral injection. Using a Walker 256 tissue-isolated tumor perfusion system, we quantified the recovery of naked plasmid DNA and cationic liposome complexes in the tumor, leakage from the tumor surface, and the venous outflow after intratumoral injection. Approximately 50% of naked plasmid DNA had been eliminated from the tumor 2 h after injection, whereas more than 90% of plasmid DNA was

retained in the tumor when it was complexed with cationic liposomes. However, the distribution of these complexes in the tumor was restricted to the tissue surrounding the injection site. Pharmacokinetic analysis of the venous outflow profiles suggested that the rate-limiting process that determines the retention of plasmid DNA in the tumor is transferred from the injection site in the tumor tissue and that complexation with cationic liposomes may retard this process. Furthermore, we examined the gene expression of chloramphenicol acetyltransferase DNA constructs (naked pCMV-CAT) and the corresponding cationic liposome (**3-beta** -(N-(N',N'-dimethylaminoethane)**carbamoyl**) **cholesterol**) complexes. A similar level of gene expression was observed in vivo after direct intratumoral injection of naked DNA and its cationic liposome complexes. In both cases, a great variation was observed between tumors, and localization of gene-transduced cells in the tumor tissue was limited to the area in the vicinity of the injection site. Thus, these pharmacokinetic and gene expression studies have demonstrated that cationic liposomes can enhance the retention of injected DNA in the tumor model, whereas cationic liposome complex does not necessarily improve gene expression because of its poor dissemination in this tumor. The present study also suggested that there is a need to control the behavior of the injected naked plasmid DNA and its cationic liposome complexes to ensure better distribution throughout the tumor.

L9 ANSWER 2 OF 39 MEDLINE DUPLICATE 1
AN 97349073 MEDLINE
TI Intratumoral pharmacokinetics and in vivo gene expression of naked plasmid DNA and its cationic liposome complexes after direct gene transfer.
AU Nomura T; Nakajima S; Kawabata K; Yamashita F; Takakura Y; Hashida M
CS Department of Drug Delivery Research, Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Japan.
SO CANCER RESEARCH, (1997 Jul 1) 57 (13) 2681-6.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9710
EW 19971001
AB The pharmacokinetic properties and gene expression of naked plasmid DNA and its cationic liposome complexes were studied after direct intratumoral injection. Using a Walker 256 tissue-isolated tumor perfusion system, we quantified the recovery of naked plasmid DNA and cationic liposome complexes in the tumor, leakage from the tumor surface, and the venous outflow after intratumoral injection. Approximately 50% of naked plasmid DNA had been eliminated from the tumor 2 h after injection, whereas more than 90% of plasmid DNA was

retained in the tumor when it was complexed with cationic liposomes. However, the distribution of these complexes in the tumor was restricted to the tissue surrounding the injection site. Pharmacokinetic analysis of the venous outflow profiles suggested that the rate-limiting process that determines the retention of plasmid DNA in the tumor is transferred from the injection site in the tumor tissue and that complexation with cationic liposomes may retard this process. Furthermore, we examined the gene expression of chloramphenicol acetyltransferase DNA constructs (naked pCMV-CAT) and the corresponding cationic liposome [**3-beta**-(N-(N',N'-dimethylaminoethane)**carbamoyl**)**cholesterol**] complexes. A similar level of gene expression was observed in vivo after direct intratumoral injection of naked DNA and its cationic liposome complexes. In both cases, a great variation was observed between tumors, and localization of gene-transduced cells in the tumor tissue was limited to the area in the vicinity of the injection site. Thus, these pharmacokinetic and gene expression studies have demonstrated that cationic liposomes can enhance the retention of injected DNA in the tumor model, whereas cationic liposome complex does not necessarily improve gene expression because of its poor dissemination in this tumor. The present study also suggested that there is a need to control the behavior of the injected naked plasmid DNA and its cationic liposome complexes to ensure better distribution throughout the tumor.

L9 ANSWER 3 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 2
AN 97:299525 BIOSIS
DN 99598728
TI Optimization of liposome mediated transfection of a neuronal cell line.
AU McQuillin A; Murray K D; Etheridge C J; Stewart L; Cooper R G; Brett P M; Miller A D; Gurling H M D
CS Molecular Psychiatry Lab., Dep. Psychiatry Behavioural Sci., UCL Med. Sch., Windeyer Inst. Med. Sci., 46 Cleveland St., London W1P 6DB, UK
SO Neuroreport 8 (6). 1997. 1481-1484. ISSN: 0959-4965
LA English
AB A cell line derived from sensory neurons was transfected with high efficiency using cationic liposomes, formulated from **3-beta**(N-(N,N'-dimethylaminoethane)**carbamoyl**)**cholesterol** (DC-Chol) and dioleoyl L-alpha-phosphatidylethanolamine (DOPE). This is the first time that cationic liposomes of this type have been reported to transfect a neuronal cell line. We used a reporter gene construct expressing beta-galactosidase under the control of the cytomegalovirus immediate early promoter and routinely observed transfection efficiencies gt 40%. Parameters affecting transfection efficiency were examined and the ratio of DNA to liposome proved to be crucial. Liposome formulation procedures and cell transfection protocols devised here will be used as a basis for further in vivo and in vitro work.

Searcher : Shears 308-4994

L9 ANSWER 4 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 3
AN 97:292762 BIOSIS
DN 99591965
TI Transfection of avian LMH-2A hepatoma cells with cationic lipids.
AU Walzem R L; Hickman M A; German J B; Hansen R J
CS Dep. Molecular Biosciences, Sch. Veterinary Med., Coll. Agricultural Environmental Sciences, Univ. California-Davis, Davis, CA 95616, USA
SO Poultry Science 76 (6). 1997. 882-886. ISSN: 0032-5791
LA English
AB LMH-2A is an estrogen-responsive avian hepatoma cell line whose susceptibility to cationic-lipid-mediated transfection is poorly described. **3-beta**(N-N',N'-dimethylaminoethane)-**carbamoyl**) **cholesterol** (DCC) requires a one-step synthesis, and can be used to formulate transfection-grade liposomes when combined with dioleoylphosphatidyl-ethanolamine (DOPE) 1/1 (wt/wt). Luciferase activities in LMH-2A cells were 8.5-fold and 87.5-fold greater than those in HepG2 and FTO2B cells, respectively, following DCC-liposome-mediated transfection with a reporter consisting of the human cytomegalovirus immediate-early promoter (CMV), joined to Photinus pyralis luciferase (L) cDNA, designated pCMVL. Using pCMVL, N-(2-bromoethyl)-N,N-dimethyl-2,3-bis(9-octadecenyloxy)-propanaminimun bromide) (BMOP)/DOPE 1/1 (wt/wt), at a 7.5:1 ratio with DNA, produced luciferase activities that were 2.9-fold higher than those of DCC-liposomes, at an optimal 10:1 lipid:DNA ratio. At optimal lipid:DNA ratios, commercially available liposomes, Transfectam, Lipofectamine, and Lipofectin, produced luciferase activities that were 1.39, 1.03, and 0.47-fold those of DCC-liposomes. The effect of 0, 10, 100, or 500 nM/L 17-beta-estradiol on the expression of pCMVL and a second luciferase reporter containing the -593/+48 promoter region of the estrogen-responsive avian apo VLDL-II gene, designated pApoL, was tested in cells cultured in the presence or absence of 10% chicken serum. The CMV promoter supported a high level of expression in LMH-2A cells that was unaffected by serum alone, but was weakly responsive to estrogen. Estrogen responses of both reporters reached a plateau at 10 nM/L. Estrogen increased the expression of pApoL 24-fold and 79-fold in the absence and presence of serum, respectively. The -593/+48 region of the apo VLDL-II promoter may not contain previously reported negative insulin response elements, but chicken serum contains factors that enhance estrogen responsiveness of this region.

L9 ANSWER 5 OF 39 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 97328161 EMBASE
TI Physicochemical properties and in vitro toxicity of cationic liposome cDNA complexes.
AU Schreier H.; Gagne L.; Bock T.; Erdos G.W.; Druzgala P.; Conary J.T.; Muller B.W.

CS H. Schreier, Advanced Therapies Inc., 371 Bel Marin Keys, Novato, CA 94949, United States. m1s86a@prodigy.com
SO Pharmaceutica Acta Helvetiae, (1997) 72/4 (215-223).
ISSN: 0031-6865 CODEN: PAHEAA
PUI S 0031-6865(97)00019-8
CY Netherlands
DT Journal
FS 022 Human Genetics
025 Hematology
029 Clinical Biochemistry
LA English
SL English
AB The purpose of this study was to elucidate the interaction of cationic liposomes and plasmid cDNA by examining their ultrastructure, zeta potential, stability in aqueous media and protection from DNaseI digestion; their potential for hemolysis and platelet aggregation was evaluated as it may serve as an in vitro toxicity screen. Liposomes consisting of N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) or 3.**beta.**-[N-(N',N'-dimethylaminoethane)-**carbamoyl**]-**cholesterol** (DC-Chol) and dioleylohosphatidylethanolamine (DOPE) were complexes with plasmid constructs of ovine prostaglandin G/H synthase (pCMV4-PGH) or human .alpha.1-antitrypsin (pCMV4-AAT) at lipid:plasmid (L/P) ratios of 3:1-8:1 (w/w). The electron micrographs showed bead-like attachment of liposomes to cDNA and coating of plasmid strands. The zeta potential showed isoelectric points at L/P ratios of 3.5-4 (DOTMA/DOPE) and 5.5-6.5, corresponding to a pK(a) of 6.45 (DC-Chol/DOPE). Liposome cDNA complexes were stable in water, saline and 5% dextrose for 48 h, but precipitated instantaneously in PBS. An increase in the L/P ratio corresponded with increased protection from DNaseI digestion. DOTMA/DOPE liposomes alone were highly hemolytic and DC-Chol/DOPE liposomes moderately hemolytic; hemolysis was abolished by cDNA complexation, with the exception of very high (.ltoreq.7:1) L/P ratios. Both liposomes alone and cDNA complexes caused transient serum turbidity, while none caused platelet aggregation. It was concluded that current cationic lipid cDNA formulations are metastable and appear to have very little if any toxicity with respect to hemolytic potential and untoward interaction with other blood components.

L9 ANSWER 6 OF 39 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.DUPLICATE 4
AN 97335961 EMBASE
TI Electrostatic parameters of cationic liposomes commonly used for gene delivery as determined by 4-heptadecyl-7-hydroxycoumarin.
AU Zuidam N.J.; Barenholz Y.
CS Y. Barenholz, Department of Biochemistry, Hebrew University, Hadassah Medical School, P.O. Box 12272, Jerusalem 91120, Israel. yb@cc.huji.ac.il

SO Biochimica et Biophysica Acta - Biomembranes, (1997) 1329/2 (211-222).
ISSN: 0005-2736 CODEN: BBBMBS
PUI S 0005-2736(97)00110-7
CY Netherlands
DT Journal
FS 039 Pharmacy
037 Drug Literature Index
LA English
SL English

AB Cationic liposomes are used to deliver genes into cells in vitro and in vivo. The present study is aimed to characterize the electrostatic parameters of cationic, large unilamellar vesicles, 110 .+-. 20 nm in size, composed of DOTAP/DOPE (mole ratio 1/1), BOTAP/DOPC (mole ratio 1/1), 100% DOTAP, DMRIE/DOPE 1/1, or DC-CHOL/DOPE (mole ratio 1/1). {Abbreviations: DOTAP, N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphatidylethanolamine; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine; DMRIE, 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethylammonium bromide; DC-CHOL, **3.beta.**[N-(N',N'-dimethylaminoethane) **carbamoyl]cholesterol**}. The cationic liposomes had a large positive surface potential and a high pH at the liposomal surface in 20 mM Hepes buffer (pH 7.4) as monitored by the pH-sensitive fluorophore 4-heptadecyl-7-hydroxycoumarin. In contrast to DOTAP and DMRIE which were 100% charged, DC-CHOL in DC-CHOL/DOPE (1/1) liposomes was only about 50% charged in 20 mM Hepes buffer (pH 7.4). This might result in an easier dissociation of bilayers containing DC-CHOL from the plasmid DNA (which is necessary to enable transcription), in a decrease of the charge on the external surfaces of the liposomes or DNA-lipid complexes, and in an increase in release of the DNA-lipid complex into the cytosol from the endosomes. Other electrostatic characteristics found were that the primary amine group of DOPE in cationic liposomes dissociated at high (> 7.9) PH(bulk) and that a salt bridge was likely between the quaternary amine of DOTAP or DMRIE and the phosphate group of DOPE or DOPC, but not between the tertiary amine of DC-CHOL and the phosphate group of DOPE. The liposomes containing DOTAP were unstable upon dilution, probably due to the high critical aggregation concentration of DOTAP, 7 x 10-5 M. This might also be a mechanism of the dissociation of bilayers containing DOTAP from the plasmid DNA.

L9 ANSWER 7 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 5
AN 97:366351 BIOSIS
DN 99658284
TI Gene transfection by cationic liposomes: Comparison of the transfection efficiency of liposomes prepared from various positively charged lipids.

AU Zhao D-D; Watarai S; Lee J-T; Kouchi S; Ohmori H; Yasuda T
CS Dep. Cell Chem., Inst. Cell. Mol. Biol., Okayama Univ. Med. Sch., Okayama 700, Japan
SO Acta Medica Okayama 51 (3). 1997. 149-154. ISSN: 0386-300X
LA English
AB We compared the transfection efficiency of four types of positively charged liposomes composed of (i) N-(alpha-trimethylammonioacetyl)-didodecyl-D-glutamate chloride (TMAG), dilauroylphosphatidylcholine (DLPC), and dioleoylphosphatidylethanolamine (DOPE) (1:2:2 molar ratio); (ii) **3-beta** (N-(N', N'-dimethylaminoethane)-**carbamoyl**) **cholesterol** (DC-Chol) and DOPE (3:2 molar ratio); (iii) dimethyldioctadecylammonium bromide (DDAB) and DOPE (1:2.2 molar ratio); (iv) N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA) and DOPE (1:1, w/w; lipofectin). Luciferase gene was used as a reporter gene. Among the cationic liposomes used, the liposomes composed of TMAG, DOPE and DLPC showed a much higher efficiency of plasmid DNA entrapment than the other cationic liposomes tested. In the absence of serum, the cationic multilamellar vesicles (MLV) and small unilamellar vesicles (SUV) composed of TMAG, DOPE and DLPC gave highly efficient transfection. On the other hand, MLV, dehydration-rehydration vesicles (DRV), and SUV liposomes prepared with the mixtures of DC-Chol and DOPE showed similar levels of transfection efficiency. However, the rationic liposomes composed of DDAB and DOPE showed inferior efficiency, whether in the form of DRV, SUV or MLV. The transfection efficiency of lipofectin was also low. In the presence of serum, on the other hand, a considerable (about 30-50%) amount of transfection activity was still observed at 10% fetal calf serum in the cationic MLV and SUV composed of TMAG, DOPE and DLPC. Cationic MLV, composed of TMAG, DOPE and DLPC, can transfect plasmid DNA, not only in the adherent cell lines but also in the suspension cell lines. These findings indicate that the transfection efficiency of cationic liposomes is affected by the lipid composition, the type of liposome, or the presence or absence of serum. They also indicate that the cationic liposomes containing TMAG, DOPE and DLPC are efficient vectors for gene transfer into cells.

L9 ANSWER 8 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 6
AN 97:219317 BIOSIS
DN 99525821
TI Lipid-mediated transfection of normal adult human hepatocytes in primary culture.
AU Ourlin J C; Vilarem M-J; Daujat M; Harricane M-C; Domergue J; Joyeux H; Baulieux J; Maurel P
CS Biozentrum der Univ. Basel Abt. Pharmakol., Klingelbergstr. 70, CH-4056 Basel, Switzerland
SO Analytical Biochemistry 247 (1). 1997. 34-44. ISSN: 0003-2697
LA English

AB The aim of this work was to develop a procedure for the lipid-mediated transfection of DNA into normal adult human hepatocytes in culture. Cells were plated in a serum-free culture medium at various cell densities, on plastic or collagen-coated dishes, both in the absence and in the presence of epidermal growth factor (EGF). The cells were incubated for various periods of time with mixtures of DNA-lipofectin or DNA-**3-beta** (N-(B',N'-dimethylaminoethane)-**carbamoyl**) **cholesterol** (DC-chol) liposomes, and the efficiency of transfection was assessed by measuring the activity of reporter genes, beta-galactosidase or chloramphenicol acetyltransferase (CAT). For comparison, similar experiments were carried out with human cell lines including HepG2, Caco-2, and WRL68. The efficiency of transfection (in percentage of cells) was not significantly different after transfection with lipofectin or DC-chol and comprised between 0.04 and 1.7% (extreme values) for different cultures. The efficiency of transfection decreased as the age or density of the culture increased and increased in cultures treated with EGF. Direct measurement of the rate of DNA synthesis suggested that the efficiency of transfection was related to the number of cells entering the S phase. Under the same conditions, the efficiency of transfection was one to two orders of magnitude greater in the three cell lines. A plasmid harboring 660 bp of the 5'-flanking region of CYP1A1 (containing two xenobioytic enhancer elements) fused upstream of the promoter of thymidine kinase and the CAT reporter gene was constructed. When this plasmid was transfected in human hepatocytes, CAT activity was induced as expected. We conclude that normal adult human hepatocytes can be transfected with exogenous DNA and that the transfected construct is regulated in the manner expected from in vivo studies.

L9 ANSWER 9 OF 39 PROMT COPYRIGHT 1997 IAC

AN 97:443621 PROMT

TI Cancer Gene Therapy "Intratumoral Pharmacokinetics and in vivo Gene Expression of Naked Plasmid DNA and Its Cationic Liposome Complexes after Direct Gene Transfer."

SO Cancer Weekly Plus, (18 Aug 1997) pp. N/A.

WC 381

FULL TEXT IS AVAILABLE IN THE ALL FORMAT

AB Nomura, T.; Nakajima, S.; Kawabata, K.; Yamashita, F.; Takakura, Y.; Hashida, M.
Cancer Research, July 1, 1997;57(13):2681-2686.
According to the authors' abstract of an article published in Cancer Research, "The pharmacokinetic properties and gene expression of naked plasmid DNA and its cationic liposome complexes were studied after direct intratumoral injection. Using a Walker 256 tissue-isolated tumor perfusion system, we quantified the recovery of naked plasmid DNA and cationic liposome complexes in the tumor,

leakage from the tumor surface, and the venous outflow after intratumoral injection. Approximately 50% of naked plasmid DNA had been eliminated from the tumor 2 h after injection, whereas more than 90% of plasmid DNA was retained in the tumor when it was complexed with cationic liposomes. However, the distribution of these complexes in the tumor was restricted to the tissue surrounding the injection site. Pharmacokinetic analysis of the venous outflow profiles suggested that the rate-limiting process that determines the retention of plasmid DNA in the tumor is transferred from the injection site in the tumor tissue and that complexation with cationic liposomes may retard this process. Furthermore, we examined the gene expression of chloramphenicol acetyltransferase DNA constructs (naked pCMV-CAT) and the corresponding cationic liposome [**3-beta**-(N-(N',N'-dimethylaminoethane)**carbamoyl**) **cholesterol**] complexes. A similar level of gene expression was observed in vivo after direct intratumoral injection of naked DNA and its cationic liposome complexes. In both cases, a great variation was observed between tumors, and localization of gene-transduced cells in the tumor tissue was limited to the area in the vicinity of the injection site. Thus, these pharmacokinetic and gene expression studies have demonstrated that cationic liposomes can enhance the retention of injected DNA in the tumor model, whereas cationic liposome complex does not necessarily improve gene expression because of its poor dissemination in this tumor. The present study also suggested that there is a need to control the behavior of the injected naked plasmid DNA and its cationic liposome complexes to ensure better distribution throughout the tumor."
The corresponding author for this study is: M Hashida, Kyoto Univ, Dept Drug Delivery Res, Fac Pharmaceut Sci, Sakyo Ku, Kyoto 60601, Japan.

L9 ANSWER 10 OF 39 PROMT COPYRIGHT 1997 IAC

AN 97:443578 PROMT
TI Cancer Gene Therapy Naked Plasmid DNA and Cationic Liposome Complexes Behave Differently In Vivo
SO Cancer Weekly Plus, (18 Aug 1997) pp. N/A.
WC 600
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB Intratumoral pharmacokinetics and in vivo gene expression differ between the direct injection of naked plasmid DNA and plasmid DNA/cationic liposome complexes.
Multiple vector systems are available for in vivo gene delivery systems. Most delivery vehicles currently in use are viral in nature. Although efficient in delivering DNA, viral vectors have several disadvantages. Nonviral vectors such as naked plasmid DNA and cationic liposome systems avoid the complications of viral

vectors, however, little is actually known about the pharmacokinetics of genes after intratumoral injection with these vectors, especially in relation to gene expression.
Japanese researchers Takehiko Nomura and colleagues quantified the recovery of naked plasmid DNA and cationic liposome complexes, leakage from tumor surface, and the venous outflow after direct tumor injection using a Walker 256 tissue-isolated tumor perfusion system ("Intratumoral Pharmacokinetics and In Vivo Gene Expression of Naked Plasmid DNA and Its Cationic Liposome Complexes After Direct Gene Transfer," Cancer Research, July 1, 1997;57(13):2681-6).
"The first objective of the present study was to evaluate the intratumoral behavior of naked plasmid DNA and its cationic liposome complex at an early phase after intratumoral injection using this perfusion system," stated Nomura et al. "The second aim of the study was to investigate the relationships between disposition characteristics and gene expression after in vivo gene transfer."
Walker 256 carcinoma tumors and female SPF Wistar rats were used the in vivo perfusion experiments, which were conducted with either naked plasmid DNA expressing the bacterial CAT gene under the control of the human CMV immediate early promoter, a plasmid control, or a corresponding cationic liposome complex **3**-(**beta**)-(N-(N'-N'-dimethylaminoethan-e)**carbamoyl**)**cholesterol**.
Within two hours of tumor injection, approximately 50 percent of the naked plasmid DNA had been eliminated from the tumor. The tumor injected with complexed cationic liposomes, however, retained more than 90 percent after the same time period. Unfortunately, the distribution of the complexes in the tumor was restricted to the tissue surrounding the injection site.
Pharmacokinetic analysis of the venous outflow profiles suggested that the rate-limiting process that determined the retention of plasmid DNA in the tumor was transferred from the injection site in the tumor tissue, noted the researchers.

L9 ANSWER 11 OF 39 DISSABS COPYRIGHT 1997 UMI Company
AN 97:40717 DISSABS Order Number: AAR9717367
TI INTERACTIONS OF LIPOSOMES AND PROTEOLIPOSOMES WITH CULTURED CELLS: APPLICATION TO THE CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (DOPE, DOTAP, CFTR)
AU HIGGINBOTHAM, CAROL ANN [PH.D.]
CS MONTANA STATE UNIVERSITY (0137)
SO Dissertation Abstracts International, (1996) Vol. 57, No. 12B, p. 7506. Order No.: AAR9717367. 162 pages.
DT Dissertation
FS DAI
LA English
AB Cystic Fibrosis (CF) is the most common fatal genetic disease affecting caucasians. Potential approaches to therapy seek to

decrease or avoid disease symptoms by correction of the genetic defect. Included in these approaches are attempts to deliver a normal copy of the defective gene, and attempts to deliver normal protein, to the affected cells of CF patients.

Liposomes composed of artificial, cationic compounds have been found to be effective DNA delivery vehicles, producing expression of the gene products introduced in a significant percentage of treated cells. This study investigated the feasibility of using liposomes for delivery of integral membrane proteins, and particularly the protein defective in CF, to cultured eukaryotic cells. Because of their demonstrated usefulness in DNA transfection, cationic liposome delivery vehicles were examined in detail.

Fluorescence microscopy was used, in conjunction with fluorescence resonance energy transfer, to characterize the interaction occurring between liposomes or proteoliposomes and cultured cells. Studies of cationic liposomes composed of dioleoylphosphatidylethanolamine (DOPE) and 1,2-bis(oleoxy)-3-(trimethylammonio) propane (DOTAP), and DOPE and **3**-$\
beta$-(N,N-dimethylaminoethane)-**carbamoyl**)
cholesterol (DC Chol) revealed that these liposomes adhered strongly to cell surfaces, but that dilution of the probes did not occur, to a measurable degree. These results suggest that these cationic liposomes would not be suitable for integral membrane protein delivery to the cell lines studied. Other liposome formulations tested did not exhibit interaction with cultured cells.

Systems employing viral envelopes (virosomes) and receptor mediated uptake of liposomes were also studied, to see if these systems might be significantly more efficient at delivery of foreign material. In the experiments performed, no evidence of lipid transfer to target cells was obtained.

The protein defective in CF is reported to undergo rapid endocytosis from the plasma membrane. To investigate the trafficking of this protein, we identified the CFTR protein by immunoblot from vesicle enriched cell fractions. Cell fractions containing clathrin, a marker protein for coated vesicles, were found also to contain a protein of approximately 170 kD which was reactive to anti-CFTR antibodies.

L9 ANSWER 12 OF 39 DISSABS COPYRIGHT 1997 UMI Company
AN 97:39721 DISSABS Order Number: AAR9715495
TI CATIONIC LIPOSOME- AND POLYMER- MEDIATED GENE TRANSFER
AU GAO, XIANG [PH.D.]; HUANG, LEAF [adviser]
CS UNIVERSITY OF PITTSBURGH (0178)
SO Dissertation Abstracts International, (1996) Vol. 57, No. 12B, p. 7360. Order No.: AAR9715495. 132 pages.
DT Dissertation
FS DAI
LA English
AB Various aspects related to the development of cationic liposome

and polymer based gene delivery systems were studied. A novel cationic lipid, **3** $**beta**$ (N-(N$\rm\sp\prime,N\sp\prime$-dimethylaminoethane) **carbamoyl**) **cholesterol** (DC-chol) was synthesized from a simple reaction with high yield. Cationic liposomes composed of DC-chol and dioleoylphosphatidylethanolamine (DOPE) showed higher transfection efficient and lower toxicity than a commercial reagent.

An excess of liposomes formed stable complexes with DNA, even at very high concentrations of both components. The complexes were purified and concentrated from the DNA/liposome mixture by ultracentrifugation on a sucrose density gradient that resulted in a single-vial, ready-to-use DNA/liposome formulation. These purified complexes were as efficient in transfection as the freshly prepared DNA/liposome complexes.

Cationic polymers dramatically reduced the particle size of the lipid/DNA complexes, rendered the DNA resistant to the nuclease activity, and enhanced the transfection activity of several types of cationic liposomes by 2-28 fold in vitro. Fractionation by ultracentrifugation obtained complexes of different amounts of lipid and different levels of transfection activity. The lipid-poor complexes were less active, unless additional free liposomes were supplemented. The lipid-enriched complexes were highly active by themselves. The purified complexes were about 3-9-fold more active than the unpurified complexes. Negative stain EM studies revealed that the purified, active complexes were all under 100 nm in size; some were associated with lipid membranes.

Finally, a potent cytoplasmic gene expression system based on a purified T7 RNA polymerase and a reporter gene driven by a T7 promoter was delivered into cells by cationic liposomes. A T7 RNA polymerase specific expression was observed that reached its peak level about eight hours sooner and 2-fold higher than a nucleus-dependent gene expression system using SV 40 enhance/promoter. The expression declined after 30 hour post-transfection. The level and the duration of the gene expression were significantly improved by the addition of a polymerase self-regenerating plasmid.

In summary, we have developed and further improved a cationic liposome based delivery technology through a series of chemical, formulational and molecular biological studies from both delivery and expression aspects.

L9 ANSWER 13 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 7
AN 97:82126 BIOSIS
DN 99373839
TI DNA-induced lateral segregation of cationic amphiphiles in lipid bilayer membranes as detected via 2H NMR.
AU Mitrakos P; MacDonald P M
CS Dep. Chem. Erindale Coll., Univ. Toronto, 3359 Mississauga Road North, Mississauga, ON, L5L 1C6, Canada
Searcher : Shears 308-4994

SO Biochemistry 35 (51). 1996. 16714-16722. ISSN: 0006-2960
LA English
AB 2H NMR spectroscopy was used to investigate the response of specifically choline-deuterated 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) to changes in surface electrostatic charge in membranes consisting of mixtures of POPC plus various cationic amphiphiles plus polyadenylic acid (polyA). Three different cationic amphiphiles were investigated: cetyltrimethylammonium bromide (CTAB), dioleoyldimethylaminopropane (DODAP), and **3-beta** (N-(N',N'-dimethylaminoethane)**carbamoyl**)**cholesterol** (DC-CHOL). Each of the cationic amphiphiles elicited a concentration-dependent decrease (increase) in the quadrupolar splitting from POPC-alpha-d-2 (POPC-beta-d-2), as expected for the accumulation of cationic charges at the surface of a lipid bilayer. However, the strength of the response varied with the cationic amphiphile in the order CTAB gt DODAP gt DC-CHOL. When polyA was added to the cationic amphiphile-containing lipid bilayers, the 2H NMR spectrum consisted of two overlapping Pake patterns, indicating the presence of two lipid domains with different effective surface charges and only slow exchange of lipids between the two domains. There was no evidence of any non-bilayer lipid arrangements. Analysis of the quadrupolar splittings of the two 2H NMR spectral components demonstrated that the polyA-containing domain was enriched with respect to cationic amphiphiles while the polyA-free domain was depleted with respect to cationic amphiphiles. We conclude that polyA is able to laterally segregate cationic amphiphiles into long-lived lipid domains of distinct composition.

L9 ANSWER 14 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 8
AN 96:230304 BIOSIS
DN 98794433
TI Folate-targeted, anionic liposome-entrapped polylysine-condensed DNA for tumor cell-specific gene transfer.
AU Lee R J; Huang L
CS Lab. Drug Targeting, Dep. Pharmacol., Univ. Pittsburgh Sch. Med., Pittsburgh, PA 15261, USA
SO Journal of Biological Chemistry 271 (14). 1996. 8481-8487. ISSN: 0021-9258
LA English
AB We have developed a lipidic gene transfer vector, LPD-II, where DNA was first complexed to polylysine at a ratio of 1:0.75 (w/w) and then entrapped into folate-targeted pH-sensitive anionic liposomes composed of dioleoyl phosphatidylethanolamine (DOPE)/ **cholesteryl** hemisuccinate/folate-polyethlene glycol-DOPE (6:4:0.01 mol/mol) via charge interaction. LPDII transfection of KB cells, a cell line overexpressing the tumor marker folate receptor, was affected by both the lipid to DNA ratio and the lipid composition. At low lipid to DNA ratios (eg. 4 and 6), LPDII particles were positively charged; transfection and cellular uptake

levels were independent of the folate receptor and did not require a pH-sensitive lipid composition. Meanwhile, transfection and uptake of negatively charged LPDII particles, i.e. those with high lipid to DNA ratios (eg. 10 and 12), were folate receptor-dependent and required a pH-sensitive lipid composition. The transfection activity of LPDII was lost when the inverted cone-shaped DOPE was replaced by dioleoyl phosphatidylcholine. LPDII particles with lipid to DNA ratios of 4, 6, 10, and 12 were apprx 20-30 times more active than DNA cntdot 3-**beta**-(N-(N',N'-dimethylethane)**carbamoyl**)**cholesterol** cationic liposome complexes in KB cells and were much less cytotoxic. On the sucrose gradient, LPDII particles had a migration rate in between those of the free DNA and the DNA cntdot polylysine complex. An electron micrograph of LPDII showed a structure of spherical particles with a positively stained core enclosed in a lipidic envelope with a mean diameter of 74 +- 14 nm. This novel gene transfer vector may potentially be useful in gene therapy for tumor-specific delivery.

L9 ANSWER 15 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 9
AN 97:65259 BIOSIS
DN 99364462
TI New cationic lipid formulations for gene transfer.
AU Liu F; Yang J; Huang L; Liu D
CS Dep. Pharm. Sci., Sch. Pharm., Univ. Pittsburgh, Pittsburgh, PA 15261, USA
SO Pharmaceutical Research (New York) 13 (12). 1996. 1856-1860. ISSN: 0724-8741
LA English
AB Purpose: To develop appropriate dosage forms of DNA for gene delivery. Methods: 3-**beta**(N-(N',N' dimethylaminoethane) **carbamoyl**) **cholesterol** (DC-Chol) was mixed either with Tween 80 alone, or with additional lipid components including castor oil and phosphatidylcholine (PC) or dioleoylphosphatidylethanolamine (DOPE) to make different lipid formulations. The particle size and the physical stability of the formulations upon mixing with plasmid DNA containing the luciferase cDNA were examined using laser light scattering measurement. The transfection activity of the DNA/lipid complexes was tested in presence or absence of serum using a cell culture system. Results: We demonstrated that many favorable properties as a gene carrier could be achieved by formulating DNA into new dosage forms using Tween 80 as the major emulsifier. Compared to the cationic liposomes, these new formulations transfected different cell lines with an equivalent or higher efficiency. Not only are they resistant to serum, but also form stable DNA complexes which could be stored for longer periods of time without losing transfection activity. Conclusions: Cationic lipids formulated into different lipid formulations using Tween 80 as a surfactant appeared to have more favorable physical and biological activities than traditional cationic liposomes as a carrier for gene

delivery.

L9 ANSWER 16 OF 39 MEDLINE DUPLICATE 10
AN 97114594 MEDLINE
TI Effect of non-ionic surfactants on the formation of DNA/emulsion complexes and emulsion-mediated gene transfer.
AU Liu F; Yang J; Huang L; Liu D
CS Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pennsylvania 15261, USA.
SO PHARMACEUTICAL RESEARCH, (1996 Nov) 13 (11) 1642-6.
Journal code: PHS. ISSN: 0724-8741.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9705
EW 19970503
AB PURPOSE: To study the structure-function relationship of non-ionic surfactants in emulsion-mediated gene delivery. METHODS: Four different types of non-ionic surfactants including Tween, Span, Brij and pluronic copolymers were used as co-emulsifiers for preparation of emulsions composed of Castor oil, dioleoylphosphatidylethanolamin e (DOPE) and 3 **beta** [N-(N', N'-dimethylaminoethane) **carbamoyl**] **cholesterol** (DC-Chol). The effect of different surfactants on the formation of DNA/emulsion complexes and transfection activity were analyzed using plasmid DNA containing luciferase cDNA as a reporter gene. RESULTS: Non-ionic surfactants containing branched polyoxyethylene chains as the hydrophilic head group were more effective in preventing the formation of large DNA/emulsion complexes than those containing one or no polyoxyethylene chain. All emulsion formulations except those containing Brij 700 exhibited high activity in transfecting mouse BL-6 cells in the absence of serum. In the presence of serum, however, transfection activity of each formulation varied significantly. Emulsions containing Tween, Brij 72, pluronic F68 and F127 demonstrated increased activity in transfecting cells in the presence of 20% serum. In contrast to emulsions containing Span, long chain polyoxyethylene of Brij showed decreased transfection activity. The particle size of the DNA/emulsion complexes and their ability to transfect cells are dependent on the concentration of non-ionic surfactant in the formulation. CONCLUSIONS: The structure of the hydrophilic head group of the non-ionic surfactants in the emulsion is important in determining how DNA molecules interact with emulsions and the extent to which DNA is transferred inside the cell.

L9 ANSWER 17 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS
AN 97:42817 BIOSIS
DN 99334805

TI Effect of non-ionic surfactants on the formation of DNA-emulsions complexes and emulsion-mediated gene transfer.
AU Liu F; Yang J; Huang L; Liu D
CS Dep. Pharm. Sci., Sch. Pharm., Univ. Pittsb., Pittsburgh, PA 15261, USA
SO Pharmaceutical Research (New York) 113 (11). 1996. 1642-1646. ISSN: 0724-8741
LA English
AB Purpose. To study the structure-function relationship of non-ionic surfactants in emulsion-mediated gene delivery. Methods. Four different types of non-ionic surfactants including Tween, Span, Brij and pluronic copolymers were used as co-emulsifiers for preparation of emulsions composed of Castor oil, dioleoylphosphatidylethanolamine (DOPE) and **3-beta**(N-(N',N'-dimethylaminoethane) **carbamoyl**) **cholesterol** (DC-Chol). The effect of different surfactants on the formation of DNA/emulsion complexes and transfection activity were analyzed using plasmid DNA containing luciferase cDNA as a reporter gene. Results. Non-ionic surfactants containing branched polyoxyethylene chains as the hydrophilic head group were more effective in preventing the formation of large DNA/emulsion complexes than those containing one or no polyoxyethylene chain. All emulsion formulations except those containing Brij 700 exhibited high activity in transfecting mouse BL-6 cells in the absence of serum. In the presence of serum, however, transfection activity of each formulation varied significantly. Emulsions containing Tween, Brij 72, pluronic F68 and F127 demonstrated increased activity in transfecting cells in the presence of 20% serum. In contrast to emulsions containing Span, long chain polyoxyethylene of Brij showed decreased transfection activity. The particle size of the DNA/emulsion complexes and their ability to transfect cells are dependent on the concentration of non-ionic surfactant in the formulation. Conclusions. The structure of the hydrophilic head group of the nonionic surfactants in the emulsion is important in determining how DNA molecules interact with emulsions and the extent to which DNA is transferred inside the cell.

L9 ANSWER 18 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 11
AN 96:564032 BIOSIS
DN 99293388
TI The use of cationic liposomes DC-CHOL-DOPE and DDAB-DOPE for direct transfer of Escherichia coli cytosine deaminase gene into growing melanoma tumors.
AU Szala S; Missol E; Sochanik A; Strozyk M
CS Dep. Tumor Biol., Inst. Oncol., 44-100 Gliwice, Poland
SO Gene Therapy 3 (11). 1996. 1026-1031. ISSN: 0969-7128
LA English
AB An attempt was made to use simple cationic liposomes DC-Chol/DOPE and DDAB/DOPE (DC-Chol is **3-beta** (N(N',N'-dimethylaminoethane) **carbamoyl**) **cholesterol**, DDAB

is dimethyldioctadecyl ammonium bromide and DOPE is dioleoylphosphatidylethanolamine) for transfer of Escherichia coli cytosine deaminase 'suicide' gene under the control of tissue-specific tyrosinase gene promoter directly into the murine melanoma B16(F10) tumor. Several repeated intratumoral injections of DNA-liposome complexes followed by intraperitoneal administrations of 5-fluorocytosine, which is converted to 5-fluorouracil, caused strong retardation of murine melanoma B16(F10) tumor growth and, in some cases, rejection of the pre-established tumor. The inhibition of tumor growth expressed as the increased survival of mice is better seen in the case of using DNA-DDAB/DOPE complexes as compared to DNA-DC-Chol/DOPE ones. It seems that the observed therapeutic effect appears to result from several factors: 5-fluorouracil generation by transfected cells, liposome toxicity (DDAB is more toxic than DC-Chol and hence more tumor cells are killed), increased transfection efficiency of surviving cancer cells (in this case DDAB is a better transfection agent than DC-Chol) and, finally, the bystander effect which causes destruction of cells untransfected with CD gene by easily diffusible 5-fluorouracil.

L9 ANSWER 19 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 12
AN 96:370369 BIOSIS
DN 99092725
TI Fate of cationic liposomes and their complex with oligonucleotide in vivo.
AU Litzinger D C; Brown J M; Wala I; Kaufman S A; Van G Y; Farrell C L; Collins D
CS Dep. Pharmacol., Amgen Inc., Thousand Oaks, CA 91320, USA
SO Biochimica et Biophysica Acta 1281 (2). 1996. 139-149. ISSN: 0006-3002
LA English
AB The present studies describe the biodistribution of cationic liposomes and cationic liposome/oligonucleotide complex following intravenous injection into mice via the tail vein. 111In-diethylenetriaminepentaacetic acid stearylamide (111In-DTPA-SA) was used as a lipid-phase radiolabel. Inclusion of up to 5 mol% DTPA-SA in liposomes composed of **3-beta**-(N-(N',N'-dimethylamino-ethane)**carbamoyl**)**cholesterol** (DC-Choi) and dioleoylphosphatidylethanolamine (DOPE) did not influence liposome formation or size, nor the binding/uptake or fusion of the cationic liposomes with CHO cells in vitro. Moreover, nuclear delivery of oligonucleotide to CHO cells was unaffected by the probe. The biodistribution of liposomes with increasing concentration of DC-Chol (1:4-4:1, DC-Chol/DOPE, mol/mol) at 24 h post-injection revealed no dependence on lipid composition. Uptake was primarily by liver, and accumulation in spleen and skin was also observed. Comparatively little accumulation occurred in lung. Clearance of injected liposomes by liver was very rapid (apprx 84.5% of the injected dose by 7.5 h post-injection). Liposome uptake

by liver and spleen were equally efficient in the dose range of 3.33 to 33.33 mg/kg body weight, yet possible saturation of liver uptake at a dose of 66.80 mg/kg may have allowed for increased spleen accumulation. Preincubation of cationic liposomes with phosphorothioate oligonucleotide induced a dramatic yet transient accumulation of the lipid in lung which gradually redistributed to liver. Similar results were observed when monitoring iodinated oligonucleotide in the complex. Immuno-histochemical studies revealed large aggregates of oligonucleotide within pulmonary capillaries at 15 min post-injection, suggesting the early accumulation in lung was due to embolism. Immuno-histochemical studies further revealed labeled oligonucleotide to be localized primarily to Kupffer cells at 24 h post-injection. Immuno-electron microscopy revealed localization of oligonucleotide primarily to the lumen of pulmonary capillaries at 15 min post-injection, and to phagocytic vacuoles of Kupffer cells at 24 h post-injection. By these methods, nuclear delivery of oligonucleotide in vivo was not observed. Increasing concentration of mouse serum inhibited cellular binding/uptake of cationic liposomes in vitro, without or with complexed oligonucleotide. We therefore postulate that interaction with plasma components, including opsonin(s), inhibits cellular uptake of the injected liposomes as well as the liposome/oligonucleotide complex, and mediates rapid uptake by Kupffer cells of the liver. These results are relevant to the design of cationic liposomes for efficient delivery of nucleic acid in vivo.

L9 ANSWER 20 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS
AN 97:115153 BIOSIS
DN 99414356
TI Large scale production of DC-Chol cationic liposomes by microfluidization.
AU Sorgi F L; Huang L
CS W1351 Biomed. Sci. Tower, Univ. Pittsburgh, Pittsburgh, PA 15261, USA
SO International Journal of Pharmaceutics (Amsterdam) 144 (2). 1996. 131-139. ISSN: 0378-5173
LA English
AB In this report, we describe the large scale production and testing of DC-Choi cationic liposomes by microfluidization. These liposomes are produced in a GMP acceptable manner to a 500 ml batch size and are shown to be sterile. Further, when stored at 4 degree C, DC-Chol liposomes will retain their original size, remain suspended in solution. and retain activity for a period exceeding 1.5 years. In-process QA and QC procedures have identified problems in processing and methods to produce a final product of pharmaceutical quality have been developed to overcome these obstacles. Assays for product content (DC-Choi and DOPE assays). size. sterility. endotoxin determination, storage conditions and shelf life have been developed. Successful lots have been used in a human gene therapy clinical trial for cystic fibrosis at Oxford University as well as many pre-clinical

experiments throughout the world. Implications for application to further gene therapy clinical trials as well as the development of liposome vector programs are discussed in detail.

L9 ANSWER 21 OF 39 BIOTECHDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-15760 BIOTECHDS
TI Efficient gene transfer to EGF receptor-overexpressing cancer cells by means of EGF-liposomes;
cationic liposome-mediated epidermal growth factor recpetor-mediated gene transfer into human endometrial carcinoma, choriocarcinoma, ovary carcinoma cell (conference abstract)
AU Kikuchi A; Sugaya S; Ueda H; Tanaka K; Aramaki Y; Hara T; Arima H; Tsuchiya S
CS Univ.Niigata; Univ.Tokyo-Pharm.
LO Department of Obstetrics and Gynecology, Niigata University School of Medicine, Niigata 951, Japan.
SO Gene Ther.; (1995) 2, 9, 687
CODEN: 4352W ISSN: 0969-7128
Japanese Society of Gene Therapy 1st Annual Meeting, Tokyo, Japan, 21 May, 1995.
DT Journal
LA English
AN 95-15760 BIOTECHDS
AB Epidermal growth factor (EGF)-labeled cationic liposomes (EGF-liposomes) including **3-beta**-(N-(N',N'-dimethylaminoethane) **carbamoyl**) **cholesterol** (DC-chol) were prepared in order to enhance liposome transfection efficiency. In HEC-1-A (human endometrial carcinoma) cells and GCH-1 (m) (human choriocarcinoma) cells, both of which have high expression of EGF receptors, EGF-liposomes induced about 2- and 4-fold higher luciferase activities than non-labeled liposomes, respectively. HRA (human ovarian carcinoma) cells, which have a low level of expression of EGF receptors, transfected with EGF-liposomes containing the luciferase gene, exhibited almost the same activities as those transfected with non-labeled liposomes. The transfection activity of the EGF-liposomes was not completely suppressed by competition with excess-free EGF, suggesting that the enhancement of the transfection activity is not only due to the increase of liposome uptake via receptor mediated endocytosis, but other mechanisms as well. (0 ref)

L9 ANSWER 22 OF 39 BIOTECHDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-03921 BIOTECHDS
TI Inhibition of human ovarian carcinoma cell proliferation by liposome-plasmid DNA complex;
plasmid pUC19 and DC-chol liposome complex lipofection for cancer gene therapy in severe combined immunodeficiency mice

AU Hofland H; *Huang L
CS Univ.Pittsburgh
LO Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA.
SO Biochem.Biophys.Res.Commun.; (1995) 207, 2, 492-96
CODEN: BBRCA9 ISSN: 0006-291X
DT Journal
LA English
AN 95-03921 BIOTECHDS
AB Severe combined immunodeficiency (SCID) mice were injected i.p. with 200 ul medium containing 30 mil human ovary carcinoma cells (2008). Treatment was initiated 2 days later at a frequency of 3 injections per wk. The mice were injected with 200 ul liposome plasmid DNA complex, which contained 50 ug plasmid pUC19 and 250 nmol **3-beta**(N-(N'N'-dimethylaminoethane)-**carbamoyl**) **cholesterol** (DC-chol) liposomes in 5% glucose. Mice injected with 250 nmol DC-chol liposomes alone, 50 ug plasmid pUC19 alone, or 5% dextrose controls. Liposome-plasmid DNA complexes appeared to inhibit the cell growth of ascites tumor cells specifically in the peritoneal cavity, while they were not toxic to the normal tissues. The inhibition of tumor growth by liposome-plasmid DNA complex was independent of the DNA sequence. Similar results were obtained using different plasmids such as plasmid pUCSV2CAT or plasmid pBR322. The sequence independent inhibition of tumor cell proliferation in vivo may augment the anti-cancer therapeutic effect of gene therapy, which depends on the gene product produced by the specific DNA sequence delivered by the liposomes. (12 ref)

L9 ANSWER 23 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS
AN 95:288149 BIOSIS
DN 98302449
TI Liposome mediated gene transfer in the gut and liver of the adult rat: Functional mapping of a eukaryotic promoter.
AU Katsel P; Mobbs C C; Greenstein R J
CS VAMC, Bronx, NY, USA
SO Clinical Research Meeting, San Diego, California, USA, May 5-8, 1995. Journal of Investigative Medicine 43 (SUPPL. 2). 1995. 331A.
DT Conference
LA English

L9 ANSWER 24 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 13
AN 95:310885 BIOSIS
DN 98325185
TI Fusion of cationic liposomes with mammalian cells occurs after endocytosis.
AU Wrobel I; Collins D
CS Dep. Pharmaceutics Drug Delivery, Mail Stop 8-1-A-215, Amgen Inc., 1840 Dehavilland Drive, Thousand Oaks, CA 91320, USA

SO Biochimica et Biophysica Acta 1235 (2). 1995. 296-304. ISSN: 0006-3002
LA English
AB The interaction of cationic liposomes prepared using either dioleoyltrimethylammonium propane (DOTAP) or **3-beta**-(N-(N',N'-dimethylaminoethane)**carbamoyl**)**cholesterol** (DC-CHOL) with model membranes and with cultured mammalian cells was examined using an assay developed for monitoring virus-cell fusion (Stegmann et al. (1993) Biochemistry 32, 11330-11337). Lipid mixing between cationic liposomes and liposomes composed of DOPE/dioleoylphosphatidylglycerol (DOPG) or dioleoylphosphatidylcholine (DOPC)/DOPG was insensitive to pH in the range of pH 4.5-7.0 and was not affected by sodium chloride concentration in the range of 0-150 mM. Lipid mixing was dependent on dioleoylphosphatidylethanolamine (DOPE), since cationic liposomes prepared using dioleoylphosphatidylcholine (DOPC) were incapable of lipid mixing with DOPC/DOPG liposomes. The interaction of cationic liposomes with Hep G-2 and CHO D- cells was also studied. For both cell types, liposome-cell lipid mixing was rapid at 37 degree C, beginning within minutes and continuing for up to 1 hour after uptake. The extent of lipid mixing was decreased at 15 degree C, especially at later (gt 20 min) time points. This suggests that at least part of the observed lipid mixing occurred after reaching cellular lysosomes. No lipid mixing was seen at 4 degree C. Monensin inhibited lipid mixing between cationic liposomes and the cells, despite having no effect on liposome uptake. Inhibition of endocytic uptake of liposomes, either by incubation in hypertonic media or by depletion of cellular ATP with sodium azide and 2-deoxyglucose abolished liposome-cell fusion in both cell types. These data demonstrate that binding to the cell surface is insufficient for cationic liposome-cell fusion and that uptake into the endocytic pathway is required for fusion to occur.

L9 ANSWER 25 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 14
AN 95:313935 BIOSIS
DN 98328235
TI The role of dioleoyl phosphatidylethanolamine in cationic liposome mediated gene transfer.
AU Farhood H; Serbina N; Huang L
CS Dep. Pharmacol., Univ. Pittsburgh Sch. Med., 13th Floor, Biomed. Sci. Tower, Pittsburgh, PA 15261, USA
SO Biochimica et Biophysica Acta 1235 (2). 1995. 289-295. ISSN: 0006-3002
LA English
AB In a reporter gene assay, cationic liposomes containing the cationic lipid **3-beta**-(N-(N',N'-dimethylaminoethane)**carbamoyl**)**cholesterol** (DC-Chol) and a neutral phospholipid dioleoylphosphatidylethanolamine (DOPE) showed high transfection activity. DNA/liposome complex which contained low

amount of liposomes could bind to the cell surface but failed to transfect the cells. We have designed a two-step protocol to examine this phenomenon in more detail. A431 human cells were incubated on ice (pulse) with DNA complexed to a low level of cationic liposomes. The cells were washed and incubated at 37 degree C (chase) with or without free cationic liposomes of various composition (helper liposomes). Only liposomes enriched with DOPE showed helper activity; liposomes containing dioleoylphosphatidylcholine (DOPC), a structural analog of DOPE, had no helper activity. The delivery was inhibited by the lysosomotropic agent chloroquine and was optimal if the helper liposome chase was initiated immediately after the pulse. An endocytosis model of DNA delivery by cationic liposomes is proposed in which the principal function of the chase liposomes is to destabilize the endosome membrane and allow the release of DNA into the cytosol. This model is consistent with the known activity of DOPE to assume non-bilayer structures, hence destabilizing the endosome membrane.

L9 ANSWER 26 OF 39 MEDLINE DUPLICATE 15
AN 96170339 MEDLINE
TI Pleotropic effects of dietary DHEA.
AU Milewich L; Catalina F; Bennett M
CS Department of Obstetrics-Gynecology and Pathology, University of Texas, Southwestern Medical Center at Dallas 75235, USA.
SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1995 Dec 29) 774 149-70.
Journal code: 5NM. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9606
AB We present data pertaining to some of the in vivo effects associated with dietary DHEA administration to mice and rats. Dietary DHEA leads to: (1) decrease in body weight gain; (2) relative increases in liver weight; (3) liver color change; (4) induction of hepatic peroxisomal enzymes; (5) proliferation of hepatic peroxisomes with increased cross-sectional area; (6) decreased hepatic mitochondrial cross-sectional area; (7) elevated levels of hepatic cytosolic malic enzyme; (8) slight decreases, significant decreases, or significant increases in serum triglyceride levels, depending on mouse strain; (9) increases in total serum **cholesterol** levels; (10) significant decreases in the hepatic rates of fatty acid synthesis; (11) significant increases in the hepatic rates of **cholesterol** synthesis; (12) decreases in both protein content and specific activity of hepatic mitochondrial **carbamoyl** phosphate synthetase-I without concomitant changes in serum urea nitrogen; (13) induction of glutathione S-transferase activity in liver; (14) decrease in hepatic endogenous protein

phosphorylation; (15) increase in hepatic AMPase and GTPase activities; (16) formation of 5-androstene-3 **beta** ,17 beta-diol as a major metabolite of DHEA by subcellular fractions of liver, which is reflected in serum and tissue levels; and (17) reduction in serum prolactin levels.

L9 ANSWER 27 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS
AN 95:77825 BIOSIS
DN 98092125
TI New structures in complex formation between DNA and cationic liposomes visualized by freeze-fracture electron microscopy.
AU Sternberg B; Sorgi F L; Huang L
CS Inst. Ultrastructure Res., Med. Sch., Friedrich-Schiller-Univ. Jena, Ziegelmuhlenweg 1, Jena D-07743, Germany
SO FEBS Letters 356 (2-3). 1994. 361-366. ISSN: 0014-5793
LA English
AB Structures formed during interaction of cationic liposomes and plasmid DNA were studied by freeze-fracture electron microscopy and their morphology was found to be dependent on incubation time and DNA concentration. These structures were formed with liposomes composed of DC-Chol and DOPE after 30 min incubation at DNA: lipid concentrations encompassing maximal transfection activity. They resembled liposome complexes (meatballs) and additionally bilayer-covered DNA tubules (spaghetti), whereby the DNA-tubules were found to be connected to the liposome complexes as well as occurring free in the suspension. At later times and higher DNA-to-liposome ratios the complexes grow larger while their membranes become discontinuous, allowing the self-encapsulation of the DNA. The relative transfection potency of the various morphologically distinct structures is discussed.

L9 ANSWER 28 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 16
AN 94:300521 BIOSIS
DN 97313521
TI Direct gene transfer by liposomes.
AU Singhal A; Huang L
CS Dep. Pharmacology, Lab. Drug Targeting, Univ. Pittsburgh, Pittsburgh, PA 15261, USA
SO Journal of Liposome Research 4 (1). 1994. 289-299. ISSN: 0898-2104
LA English
AB Cationic liposomes are widely used for the delivery of genes both in vivo and in clinical trials. DC-chol liposome formulation was developed by us for relatively high activity of transfection and low level of toxicity for most cell types. Different strategies are described for achieving regulated transgene expression as well as expression for a prolonged period of time using DC-chol liposomes.

L9 ANSWER 29 OF 39 BIOTECHDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-02113 BIOTECHDS

TI Cationic liposomes for direct gene transfer in therapy of cancer and other diseases;
lipofection for melanoma therapy (conference paper)

AU Farhood H; Gao X; Son K; Yang Y Y; Lazo J S; Huang L; Barsoum J; Bottega R; Epand R M

CS Univ.Pittsburgh; Biogen; Univ.McMaster

LO Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA.

SO Ann.N.Y.Acad.Sci.; (1994) 716, 23-35
CODEN: ANYAA9 ISSN: 0077-8923
Gene Therapy for Neoplastic Diseases, Washington DC, USA, 27-29 June, 1993.

DT Journal

LA English

AN 95-02113 BIOTECHDS

AB Cationic liposomes complex to negatively charged naked DNA resulting in a net positive charge. Transfection is highly efficient. To improve gene delivery, cationic **cholesterol** derivatives were synthesized. Results showed a connection between their structure, toxic effects, transfection activity, and effect on protein-kinase-C. Tertiary amines were most efficient but had a reduced shelf life. This led to synthesis of a derivative termed **3 beta** [N-(N',N'-dimethylaminoethane)-**carbamoyl**] **cholesterol** (DC-Chol). DNA carriers were developed. The level, onset and termination of gene expression was studied. T7 RNA polymerase and HIV virus trans-activator (tat) protein were tested. Little cytoplasmically derived DNA reached the nucleoplasm. Cytoplasmic transcription in mammalian cells was substantiated using bacteriophage T7 RNA polymerase. tat Protein delivery to cultured cells was tested, codelivery with DNA coding for a reporter gene was efficient. Tumor cells selected for cis-platin resistance were transfectable with cationic liposomes. In vivo delivery of DC-Chol liposomes for treatment of melanoma was recently approved. (29 ref)

L9 ANSWER 30 OF 39 BIOTECHDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 93-06139 BIOTECHDS

TI Method for delivering nucleic acid into cell;
liposome composition containing cationic lipid with cholesterol group, linker, spacer arm, cationic amino group, for use in mammal cell culture transfection by lipofection

PA Univ.Tenn.Res.Corp.

PI WO 9305162 18 Mar 1993

AI WO 92-US7290 28 Aug 1992

PRAI US 91-751873 28 Aug 1991

DT Patent

LA English

OS WPI: 93-100985 [12]

AN 93-06139 BIOTECHDS

AB A new method for transfer of nucleic acids into mammal cells via transfection (lipofection) involves treating cells with a dispersion containing nucleic acids and a mixed lipid dispersion of a cationic lipid with a co-lipid in a solvent. The cationic lipid includes a lipophilic **cholesterol** group, a carboxyamide or **carbamoyl** linker, a linear or branched C1-20 alkyl spacer arm, and a cationic primary, secondary, tertiary or quaternary amino group. The cationic lipid is a weak protein-kinase-C-inhibitor, and the co-lipid may be lecithin, phosphatidylethanolamine or dioleoyl phosphatidylethanolamine. The cationic lipid dispersion preferably has particles with an average diameter of 150 nm. The solvent may be distilled water, normal saline or buffered saline. The cationic lipid may be **cholesteryl**- **3-beta**-carboxyamidoethylene trimethylammonium iodide, **cholesteryl** - **3-beta**-carboxyamidoethyleneamine, **cholesteryl**- **3-beta**-oxysuccinamidoethylene trimethylammonium iodide, **3-beta**-(N-(N'N'-dimethylaminoethane) **carbamoyl**) **cholesterol** or **3-beta**-(N-(polyethyleneimine)- **carbamoyl**) **cholesterol**. (40pp)

L9 ANSWER 31 OF 39 BIOTECHDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 93-11003 BIOTECHDS
TI Cationic liposomes and polymers for gene transfer; cationic liposome and polylysine polymer application in transfection, lipofection for e.g. gene therapy; a review
AU Gao X; *Huang L
LO Department of Pharmacology, University of Pittsburgh School of Medici ne, Pittsburgh, PA 15261, USA.
SO J.Liposome Res.; (1993) 3, 1, 17-30
CODEN: JLREE7
DT Journal
LA English
AN 93-11003 BIOTECHDS
AB Cationic liposome and polylysine polymer application in transfection for e.g. gene therapy is reviewed with respect to: (1) dioleoyl-phosp hatidylethanolamine (DOPE):quaternary amino detergent cationic liposo mes; (2) DOPE:DC-Chol (**3-beta**-(N',N'-dimethylaminoethane)**carbamoyl** ch olesterol) cationic liposomes; (3) protein-kinase-C inhibitory activi ty, toxicity and transfection activity of other **cholesterol** derivativ es; and (4) targeted polycations as DNA delivery vehicles (lipopolyly sine and lipopolylysine-containing liposome-mediated gene transfectio n, and N-terminal modified polylysine-antibody conjugates as carriers for targeted gene delivery in vitro and in vivo). The cationic lipo some formulation DC-chol:DOPE is being used in clinical trials for ca

ncer gene therapy. (27 ref)

L9 ANSWER 32 OF 39 DRUGU COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 92-42284 DRUGU B P G
TI Cationic Liposomes Enhance Targeted Delivery and Expression of Exogenous DNA Mediated by N-Terminal Modified Poly(L-lysine)-Antibody Conjugate in Mouse Lung Endothelial Cells.
AU Trubetskoy V S; Torchilin V P; Kennel S; Huang L
LO Knoxville, Oak Ridge, Tennessee, United States
SO Biochim.Biophys.Acta N (1131, No. 3, 311-13, 1992) 3 Fig. 11 Ref.
CODEN: BBGSD5 ISSN: 0167-4781
AV Center for Imaging and Pharmaceutical Research, Massachusetts General Hospital, Building 149, 13th Street, Charlestown, MA 02129, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 92-42284 DRUGU B P G
AB A ternary complex composed of anti-thrombomodulin antibody, 34A-N-terminal modified poly(L-lysine) (NPLL) carrying pUCSV2 chloramphenicol acetyltransferase (CAT) plasmids and cationic liposomes (CL) showed significantly enhanced transfection activity in mouse lung endothelial cells increasing the non-specific transfection level. The binary complex containing only 34A-NPLL/DNA exhibited only low transfection activity. The results indicate that inclusion of CL into the complex enhances the frequency of endosome destabilization which results in an increased amount of DNA release into the cytoplasm and may be useful in transgene delivery and gene therapy.
ABEX CL containing 65 mol% **3 beta** (N-(N',N'-dimethyl aminoethane)**carbamoyl**) **cholesterol** and 35 mol% dioleoylphosphatidyl ethanolamine were prepared. Addition of 34A-NPLL to the CL/DNA binary complex increased the binding of 32P-DNA to mouse lung endothelial cells, which was partially inhibited by the presence of free 34A antibody. Addition of Ig14-NPLL to the CL/DNA complex decreased the non-specific binding of DNA to the cells. The CAT activity of cells transfected with the binary complex was low. Increasing the amount of CL increased CAT activity 10- to 20-fold in the transfected cells. When the ratio of Ab-NPLL to CL was 1.2, there was a 10-fold difference in the CAT activity between cells transfected with specific 34A-NPLL/CL/DNA and those with the non-specific 14-NPLL/CL/DNA complexes. (M59/TOB)

L9 ANSWER 33 OF 39 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 17
AN 91:478176 BIOSIS
DN BA92:111936
TI A NOVEL CATIONIC LIPOSOME REAGENT FOR EFFICIENT TRANSFECTION OF

MAMMALIAN CELLS.
AU GAO X; HUANG L
CS DEP. BIOCHEM., UNIV. TENN., KNOXVILLE, TENN. 37996-0840.
SO BIOCHEM BIOPHYS RES COMMUN 179 (1). 1991. 280-285. CODEN: BBRCA9
ISSN: 0006-291X
LA English
AB A novel cationic derivative of **cholesterol**, **3**.
beta.[N-(N',N'-dimethylaminoethane)-**carbamoyl**]
cholesterol (DC-Chol), has been synthesized and used to prepare sonicated liposomes with dioleoylphosphatidylethanolamine. This novel cationic liposome reagent facilitates efficient DNA mediated transfection in A431 human epidermoid carcinoma cells, A549 human lung carcinoma cells, L929 mouse fibroblast cells, and YPT minipig primary endothelial cells. The activity was greater than that of a commercial reagent, Lipofectin, and was approximately 4-fold less toxic than Lipofectin when assayed with A431 cells. The reagent is easy to synthesize and stable for at least 6 weeks.

L9 ANSWER 34 OF 39 DRUGU COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 83-24512 DRUGU B
TI C-22-Substituted Steroid Derivatives as Substrate Analogues and Inhibitors of Cytochrome P-450scc.
AU Sheets J J; Vickery L E
LO Irvine, California, United States
SO J.Biol.Chem. (258, No. 3, 1720-25, 1983) 8 Fig. 40 Ref.
CODEN: JBCHA3 ISSN: 0021-9258
AV Department of Physiology and Biophysics, University of California, Irvine, California 92717, U.S.A.
LA English
DT Journal
FA AB; LA; CT; MPC
FS Literature
AN 83-24512 DRUGU B
AB The cholesterol analog 22-amino- 23,24-bisnor- 5-cholen-3-beta-ol (22 -ABC) was a potent inhibitor of the side chain cleavage of cholesterol to produce pregnenolone catalyzed by purified adrenocortical cytochrome P-450scc. Spectral and kinetic data concerning 22-ABC, the 5-alpha-cholan- 3-beta-ol derivative (5-alpha -22-ABC) and the 22-hydroxy analog (22-diol) supported the previously published model in which the inhibitor interacted with the substrate and with the heme catalytic site simultaneously.
ABEX Cytochrome P-450scc, adrenodoxin and adrenodoxin reductase were purified from bovine adrenal cortex. **Cholesterol** side chain cleavage was measured in mixtures containing Tween 20, adrenodoxin, adrenodoxin reductase and an NADPH-generating system. Pregnenolone was determined by RIA. 22-ABC was prepared from 23,24-bisnor-5 -cholenic acid-**3**-**beta**-ol acetate (Steraloids) via the acid chloride, **carboxamide** acetate and **carboxamide**. 5-Alpha-22-ABC was prepared from

23,24-bisnor- 5-alpha- cholan-**3-beta**-ol (Steraloids). Binding of 22-ABC or 5-alpha-22-ABC to cytochrome P-450scc caused a shift in the Soret absorption maximum to 422 nm. A similar shift was observed for the interaction of enzyme and 4 -phenylimidazole. Binding of 22-diol to the enzyme produced a Soret peak at 417 nm. In the presence of 70 uM **cholesterol** , I50 values for 22-ABC, 5-alpha-22-ABC and 22-diol were 0.1, 3 and 15 uM, respectively. Difference spectra produced during titration of 5 -alpha-22-ABC and enzyme in the presence of Tween 20 yielded a spectral dissociation constant of 9 uM, reduced to 3.8 uM in the presence of adrenodoxin. The data were consistent with coordination of the 22-amino group leading to formation of the 422 nm spectral species. The 5-androstene ring determined affinity but not the type of spectral complex. The lower potency of 22-diol emphasized the importance of the 22-amino group for high affinity binding and the formation of the 422 nm spectral species.

L9 ANSWER 35 OF 39 DRUGB COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 80-02394 DRUGB C P S
TI POTENTIAL ANTICANCER AGENTS, XIX. NEW URETHANIC TYPE NITROGEN MUSTARDS DERIVED FROM STEROIDIC STRUCTURES.
AU NICULESCU DUVAZ I; ELIAN I; IONESCU M; TARNAUCEANU E
LO BUCHAREST, RUM.
SO J.PRAKT.CHEM. (321, NO.3, 522-28, 1979)
LA German
DT Journal

L9 ANSWER 36 OF 39 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 77047132 EMBASE
TI Identification by physical means of organic moieties of conjugates produced from carbaryl by tobacco cells in suspension culture.
AU Locke R.K.; Chen J.Y.T.; Damico J.N.; et al.
CS Div. Toxicol., Food Drug Adm., USDHEW, Washington, D.C. 20204, United States
SO ARCH.ENVIRON.CONTAM.TOXICOL., (1976) 4/1 (60-100). CODEN: AECTCV
LA English
AB Carbaryl (1 naphthyl methylcarbamate), labeled with 14C in the C1 naphthyl, carbonyl, or N methyl position, was introduced into the culture medium to tobacco cells in suspension culture. Following incubation, cells were homogenized in water, centrifuged, and supernatants hydrolyzed with .beta. glucosidase or HCl. Organic moieties (moieties) were characterized by two dimensional thin layer chromatography (TLC), and many were subsequently identified by infrared and mass spectrometry. On the basis of the data obtained with 14C1 naphthyl labeled carbaryl, it appeared that 18.4% of the total characterized metabolites represented unconjugated N CH2OH carbaryl [1 naphthyl N (hydroxymethyl)**carbamate**], excreted by the cells into the culture medium. The metabolites found in the

cells primarily consisted of conjugates of 1 naphthol (73.6% of the total characterized metabolites) and N CH2OH carbaryl (2.5%). Conjugates of 7 hydroxycarbaryl (7 hydroxy 1 naphthyl methylcarbamate), 4 hydroxycarbaryl (4 hydroxy 1 naphthyl methylcarbamate), and 5 hydroxycarbaryl (5 hydroxy 1 naphthyl methylcarbamate) were also detected in small amounts. Of five unknown 14C1 naphthyl labeled carbaryl metabolites, three were tentatively characterized as: O 1 naphthylcholesterol (cholest 5 en 3.**beta**. yl 1 naphthol; 3.0%); an unconjugated hydroxylated 1,4 dihydro 1,4 epiperoxynaphthalene (1.4%); and an acid labile, .beta. glucosidase resistant conjugate of a cis dihydrodiol of 1 naphthol (0.3%; other than the trans 5,6 dihydrodiol). The **cholesterol** derivative may represent a new 'detoxification mechanism' in plants; the epiperoxide may help to elucidate plant oxidation mechanisms. A new TLC procedure was developed which successfully separated the acetate derivative of N hydroxycarbaryl (1 naphthyl N hydroxy N methylcarbamate) from 12 other common moieties of carbaryl metabolites and their acetate derivatives. A new two dimensional TLC system was developed for the separation of underivatized N hydroxycarbaryl from 14 other moieties of carbaryl metabolites; two additional two dimensional TLC systems were utilized for moiety separations. With these TLC procedures, no conjugated or unconjugated N hydroxycarbaryl could be detected in any tobacco cell culture fraction after incubation of cells in medium containing radiolabeled carbaryl. Authentic 14C1 naphthyl labeled N CH2OH carbaryl was shown to be converted to desmethylcarbaryl (1 naphthylcarbamate) (97%) and 1 naphthol (3%) by 0.1N HCl hydrolysis.

L9 ANSWER 37 OF 39 DRUGB COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 76-25673 DRUGB C
TI 3-BROMO-4,4-DIMETHYL-2-OXAZOLIDINONE PREPARATION AND INVESTIGATION OF A NEW BROMINATING AGENT.
AU KAMINSKI J J; BODOR N
CS INTERX
LO LAWRENCE,KANS.,USA.
SO TETRAHEDRON (32, NO.10, 1097-99, 1976)
DT Journal

L9 ANSWER 38 OF 39 DRUGB COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 68-07542 DRUGB C
TI REACTIONS OF LEAD TETRAACETATE. I. FORMATION OF ACYLAMINES FROM PRIMARY CARBOXAMIDES. II. FORMATION OF CARBAMIC ACID ESTERS FROM PRIMARY CARBOXAMIDES.
AU ACOTT B; BECKWITH A L J; HASSANALI A
LO ADELAIDE,AUSTR.
SO AUSTRALIAN J.CHEM. (21, NO.1, 185-205, 1968)
DT Journal

Searcher : Shears 308-4994

L9 ANSWER 39 OF 39 DRUGB COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 66-25945 DRUGB B
TI MYOTONIC RESPONSE INDUCED BY INHIBITORS OF CHOLESTEROL BIOSYNTHESIS.
AU WINER N; KLACHKO D M; BAER R D; LANGLEY P L; BURNS T W
LO COLUMBIA,MO.
SO SCIENCE (153, NO.3733, 312-13, 1966)
DT Journal

FILE 'USPATFULL' ENTERED AT 16:25:59 ON 15 DEC 1997
CA INDEXING COPYRIGHT (C) 1997 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 9 Dec 1997 (19971209/PD)
FILE LAST UPDATED: 10 Dec 1997 (971210/ED)
HIGHEST PATENT NUMBER: US5697097
CA INDEXING IS CURRENT THROUGH 10 Dec 1997 (971210/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 9 Dec 1997 (19971209/PD)
REVISED CLASS FIELDS (/NCL) CURRENT THROUGH: AUG 1997
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: JUN 1997

>>> Page images are available for patents from 1/1/94. Current <<<
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>>> page images are available for display by the end of the day. <<<
>>> Image data for the /FA field are available the following week. <<<

>>> Complete CA file indexing for chemical patents (or equivalents) <<<
>>> is included in file records. A thesaurus is available for the <<<
>>> USPTO Manual of Classifications in the /NCL, /INCL, and /RPCL <<<
>>> fields. This thesaurus includes catchword terms from the <<<
>>> USPTO/MOC subject headings and subheadings. Thesauri are also <<<
>>> available for the WIPO International Patent Classification <<<
>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4, <<<
>>> /IC5, and /IC (/IC6) fields, respectively. The thesauri in <<<
>>> the /IC5 and /IC fields include the corresponding catchword <<<
>>> terms from the IPC subject headings and subheadings. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

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  13667 CHOLESTER?
2208423 3
 160616 BETA
    377 BETAS
 160693 BETA
          (BETA OR BETAS)
1098828 B
  36212 CARBAM?
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Searcher : Shears 308-4994

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         10978 CARBOXAMID?
        188230 CARBOX?
        106677 AMID?
          1557 CARBOX? AMID?
                 (CARBOX?(W)AMID?)
L10         59 L7(S)(CARBAM? OR CARBOXAMID? OR CARBOX? AMID?)

=> s l10 and (immuniz? or immunis? or adjuvant# or vaccin?)

          8205 IMMUNIZ?
           517 IMMUNIS?
         31146 ADJUVANT#
          7381 VACCIN?
L11          5 L10 AND (IMMUNIZ? OR IMMUNIS? OR ADJUVANT# OR VACCIN?)

=> d 1-5 bib abs; fil hom


L11  ANSWER 1 OF 5  USPATFULL
AN     97:56335  USPATFULL
TI     Methods for the suppression of neu mediated tumors by adenoviral
       E1A and SV40 large T antigen
IN     Hung, Mien-Chie, Houston, TX, United States
       Yu, Di-Hua, Houston, TX, United States
       Matin, Angahin, Houston, TX, United States
       Zhang, Yujiao Joe, Houston, TX, United States
PA     Board of Regents, The University of Texas System, Austin, TX,
       United States (U.S. corporation)
PI     US 5643567  970701
AI     US 94-276359  940715 (8)
RLI    Continuation-in-part of Ser. No. US 93-162406, filed on 3 Dec 1993
       which is a continuation-in-part of Ser. No. US 93-70410, filed on
       4 Jun 1993 which is a continuation-in-part of Ser. No. US
       90-621465, filed on 4 Dec 1990, now abandoned
DT     Utility
EXNAM  Primary Examiner: Crouch, Deborah
LREP   Arnold, White & Durkee
CLMN   Number of Claims: 22
ECL    Exemplary Claim: 1
DRWN   69 Drawing Figure(s); 40 Drawing Page(s)
LN.CNT 3385
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Disclosed are methods and compositions for the suppression of
       expression of the neu oncogene, as well as suppression of neu
       oncogene-mediated transformation, tumorigenesis and metastasis.
       The method disclosed involves introduction of adenovirus early 1A
       gene (the E1A gene) products, or the large T antigen (the LT gene
       product), or both into affected cells. These products, which are
       preferably introduced by transfection of the E1A gene into
```

affected cells, serve to suppress neu gene expression as measured by a reduction of p185 expression. Furthermore, the E1A gene products surprisingly serve to suppress the oncogenic phenotype, as indicated by a reduction in cell growth, growth in soft agar, as well as tumorigenic and metastatic potential in vivo. The inventors propose that E1A gene products, LT gene products or derivatives therefrom, may ultimately be employed a treatment modalities for neu-mediated cancers, such as cancers of the female genital tract and breast. The inventors also propose methods of transfecting cells with either the E1A or the LT gene products using adenoviral vectors or liposomes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 2 OF 5 USPATFULL
AN 97:53936 USPATFULL
TI Methods for the suppression of neu mediated tumors by adenoviral E1A and SV40 large T antigen
IN Hung, Mien-Chie, Houston, TX, United States
Yu, Di-Hua, Houston, TX, United States
Matin, Angabin, Houston, TX, United States
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
PI US 5641484 970624
AI US 93-162406 931203 (8)
RLI Continuation-in-part of Ser. No. US 93-70410, filed on 4 Jun 1993 which is a continuation-in-part of Ser. No. US 90-621465, filed on 4 Dec 1990, now abandoned
DT Utility
EXNAM Primary Examiner: Crouch, Deborah
LREP Arnold, White & Durkee
CLMN Number of Claims: 43
ECL Exemplary Claim: 1
DRWN 54 Drawing Figure(s); 31 Drawing Page(s)
LN.CNT 3192
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are methods and compositions for the suppression of expression of the neu oncogene, as well as suppression of neu oncogene-mediated transformation, tumorigenesis and metastasis. The method disclosed involves introduction of adenovirus early 1A gene (the E1A gene) products, so to large T antigen (the LT gene product), or both into affected cells. These products, which are preferably introduced by transfection of the E1A gene into affected cells, serve to suppress neu gene expression as measured by a reduction of p185 expression. Furthermore, the E1A gene products surprisingly serve to suppress the oncogenic phenotype, as indicated by a reduction in cell growth, growth in soft agar, as well as tumorigenic and metastatic potential in vivo. The inventors propose that E1A gene products, LT gene products or

derivatives therefrom, may ultimately be employed a treatment modalities for neu-mediated cancers, such as cancers of the female genital tract and breast. The inventors also propose methods of transfecting cells with either the E1A or the LT gene products using liposomes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 3 OF 5 USPATFULL
AN 95:94826 USPATFULL
TI Production of immunoproximity catalysts
IN Kim, Peter S., Brookline, MA, United States
Kallenbach, Neville R., New York, NY, United States
PA IGEN, Inc., Gaithersburg, MD, United States (U.S. corporation)
PI US 5460960 951024
AI US 94-187810 940127 (8)
RLI Continuation of Ser. No. US 92-857683, filed on 25 Mar 1992, now abandoned which is a continuation of Ser. No. US 87-92230, filed on 2 Sep 1987, now abandoned
DT Utility
EXNAM Primary Examiner: Patterson, Jr., Charles L.
LREP Curtis, Morris & Safford; Evans, Barry
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 645
AB Process for producing an immunoproximity catalyst for a chemical reaction. Chemical reactions in which the immunoproximity catalyst can be used are also disclosed.

L11 ANSWER 4 OF 5 USPATFULL
AN 95:34082 USPATFULL
TI Phencyclidine and phencyclidine metabolites assay, tracers, immunogens, antibodies and reagent kit
IN Dubler, Robert E., Gurnee, IL, United States
Frintner, Mary P., Elk Grove, IL, United States
Grote, Jonathan, Grayslake, IL, United States
Hadley, Gregg A., St. Louis, MO, United States
Hawksworth, David J., Vernon Hills, IL, United States
Hopkins, Hal D., Chicago, IL, United States
Nam, Daniel S., Lake Elsinore, CA, United States
Ungemach, Frank S., Lake Villa, IL, United States
Wray, Larry K., Highland Park, IL, United States
PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)
PI US 5407834 950418
AI US 92-831762 920427 (7)
RLI Division of Ser. No. US 90-529988, filed on 29 May 1990, now

patented, Pat. No. US 5155212 which is a continuation-in-part of Ser. No. US 86-866193, filed on 21 May 1986, now abandoned
DT Utility
EXNAM Primary Examiner: Kim, Kay K. A.
LREP Pope, Lawrence S.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 32 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 1662
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to a fluorescence polarization assay for phencyclidine and phencyclidine derivatives, to the various components needed for preparing and carrying out such an assay, and to methods of making these components. Specifically, tracers, immunogens and antibodies are disclosed, as well as methods for making them, and a reagent kit containing them. The tracers and the immunogens are made from substituted phencyclidine compounds. A fluorescein moiety is included in the tracer, while a poly(amino acid) forms a part of the immunogen. The assay is conducted by measuring the degree of polarization retention of plane polarized light that has been passed through a sample containing antiserum and tracer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 5 OF 5 USPATFULL
AN 92:84969 USPATFULL
TI Phencyclidine and phencyclidine metabolites assay, tracers, immunogens, antibodies and reagent kit
IN Dubler, Robert E., Gurnee, IL, United States
Frintner, Mary P., Elk Grove, IL, United States
Grote, Jonathan, Grayslake, IL, United States
Hadley, Gregg A., St. Louis, MO, United States
Hawksworth, David J., Vernon Hills, IL, United States
Hopkins, Hal D., Chicago, IL, United States
Nam, Daniel S., Lake Elsinore, CA, United States
Ungemach, Frank S., Lake Villa, IL, United States
Wray, Larry K., Highland Park, IL, United States
PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)
PI US 5155212 921013
AI US 90-529988 900529 (7)
RLI Continuation-in-part of Ser. No. US 86-866193, filed on 21 May 1986, now abandoned
DT Utility
EXNAM Primary Examiner: Nucker, Christine; Assistant Examiner: Kim, Kay K.
LREP Breininger, Thomas M.
CLMN Number of Claims: 3

ECL Exemplary Claim: 1
DRWN 32 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 1511
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to a fluorescence polarization assay for phencyclidine and phencyclidine derivatives, to the various components needed for preparting and carrying out such an assay, and to methods of making these components. Specifically, tracers, immunogens and antibodies are disclosed, as well as methods for making them, and a reagent kit containing them. The tracers and the immunogens are made from substituted phencyclidine compounds. A fluorescein moiety is included in the tracer, while a poly(amino acid) forms a part of the immunogen. The assay is conducted by measuring the degree of polarization retention of plane polarized light that has been passed through a sample containing antiserum and tracer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

FILE 'HOME' ENTERED AT 16:27:37 ON 15 DEC 1997

=> fil ca,caplus

FILE 'CA' ENTERED AT 16:30:55 ON 15 DEC 1997
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'CAPLUS' ENTERED AT 16:30:55 ON 15 DEC 1997
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

=> s dc chol

L12 79 DC CHOL

=> s l12(s)cholest?

L13 32 L12(S) CHOLEST?

=> s l13 not l5

L14 1 L13 NOT L5

=> d .bevstr1

L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1997 ACS
AN 1997:674204 CAPLUS
TI Anti-inflammatory activity of cationic lipids
AU Filion, Mario C.; Phillips, Nigel C.
CS Faculte de Pharmacie, Universite de Montreal, Montreal, PQ, H3C 3J7, Can.
SO Br. J. Pharmacol. (1997), 122(3), 551-557
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB The effect of liposome phospholipid compn. has been assumed to be relatively unimportant because of the presumed inert nature of phospholipids. We have previously shown that cationic liposome formulations used for gene therapy inhibit, through their cationic component, the synthesis by activated macrophages of the pro-inflammatory mediators nitric oxide (NO) and tumor necrosis factor-.alpha. (TNF-.alpha.). In this study, we have evaluated the ability of different cationic lipids to reduce footpad inflammation induced by carrageenan and by sheep red blood cell challenge. Parenteral (i.p. or s.c) or local injection of the pos. charged lipids dimethyldioctadecylammomium bromide (DDAB), dioleyoltrimethylammonium propane (DOTAP), dimyristoyltrimethylammonium propane (DMTAP) or dimethylaminoethanecarbamoyl **cholesterol** (**DC-Chol**) significantly reduced the inflammation obsd. in both models in a dose-dependent manner (max. inhibition: 70-95%). Cationic lipids assocd. with dioleyol- or dipalmitoyl-phosphatidylethanolamine retained their anti-inflammatory activity while cationic lipids assocd. with dipalmitoylphosphatidylcholine (DPPC) or dimyristoylphosphatidylglycerol (DMPG) showed no anti-inflammatory activity, indicating that the release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity. The anti-inflammatory activity of cationic lipids was abrogated by the addn. of dipalmitoylphosphatidylethanolamine-poly(ethylene)glycol-2000 (DPPE-PEG2000) which blocks the interaction of cationic lipids with macrophages. Because of the significant role of protein kinase C (PKC) in the inflammatory process we have detd. whether the cationic lipids used in this study inhibit PKC activity. The cationic lipids significantly inhibited the activity of PKC but not the activity of a non-related protein kinase, PKA. The synthesis of interleukin-6 (IL-6), which is not dependent on PKC activity for its induction in macrophages, was not modified in vitro or in situ by cationic lipids. The synthesis of NO and TNF-.alpha. in macrophages, both of which are PKC-dependent, was downregulated by cationic lipids. These results demonstrate that cationic lipids can be considered as novel anti-inflammatory agents. The downregulation of pro-inflammatory mediators through interaction of cationic lipids

with the PKC pathway may explain this anti-inflammatory activity. Furthermore, since cationic lipids have intrinsic anti-inflammatory activity, cationic liposomes should be used with caution to deliver nucleic acids for gene therapy in vivo.

IT Gene therapy
(anti-inflammatory activity of cationic lipids in relation to liposome-mediated gene therapy)

IT Anti-inflammatory drugs
(anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

IT Tumor necrosis factor .alpha.
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

IT Liposomes (drug delivery systems)
(cationic; anti-inflammatory activity of cationic lipids in relation to liposome-mediated gene therapy)

IT Lipids
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic; anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

IT Macrophage
(cytoplasm, interaction with; anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

IT Cytoplasm
(macrophage, interaction with; anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

IT 2390-68-3, DDAB 137056-72-5
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

IT 144189-73-1, DOTAP
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

IT 10102-43-9, Nitric oxide 141436-78-4, Protein kinase C
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(anti-inflammatory activity of cationic lipids through interaction with protein kinase C pathway)

=> d his l15

Searcher : Shears 308-4994

(FILE 'BIOSIS, MEDLINE, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, DISSABS, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGB, DRUGNL, DRUGLAUNCH' ENTERED AT 16:32:49 ON 15 DEC 1997)

L15 80 S L13

=> s l15 and (immuniz? or immunis? or adjuvant# or vaccin?)

L16 1 L15 AND (IMMUNIZ? OR IMMUNIS? OR ADJUVANT# OR VACCIN?)

=> s l16 not l8

L17 1 L16 NOT L8

=> d bib abs; fil uspat; s l13

L17 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 1997 ISI (R)
AN 97:752114 SCISEARCH
GA The Genuine Article (R) Number: XZ409
TI Anti-inflammatory activity of cationic lipids
AU Filion M C; Phillips N C (Reprint)
CS UNIV MONTREAL, FAC PHARM, CP 6128, SUCC CTRVILLE, MONTREAL, PQ H3C 3J7, CANADA (Reprint); UNIV MONTREAL, FAC PHARM, MONTREAL, PQ H3C 3J7, CANADA
CYA CANADA
SO BRITISH JOURNAL OF PHARMACOLOGY, (OCT 1997) Vol. 122, No. 3, pp. 551-557.
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE, HAMPSHIRE, ENGLAND RG21 6XS.
ISSN: 0007-1188.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 59
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB 1 The effect of liposome phospholipid composition has been assumed to be relatively unimportant because of the presumed inert nature of phospholipids.

2 We have previously shown that cationic liposome formulations used for gene therapy inhibit, through their cationic component, the synthesis by activated macrophages of the pro-inflammatory mediators nitric oxide (NO) and tumour necrosis factor-alpha (TNF-alpha).

3 In this study, we have evaluated the ability of different cationic lipids to reduce footpad inflammation induced by carrageenan and by sheep red blood cell challenge.

4 Parenteral (i.p. or s.c) or local injection of the positively charged lipids dimethyldioctadecylammomium bromide (DDAB), dioleyoltrimethylammonium propane (DOTAP),

dimyristoyltrimethylammonium propane (DMTAP) or dimethylaminoethanecarbamoyl **cholesterol** (**DC-Chol**) significantly reduced the inflammation observed in both models in a dose-dependent manner (maximum inhibition: 70-95%).

5 Cationic lipids associated with dioleyol- or dipalmitoyl-phosphatidylethanolamine retained their antiinflammatory activity while cationic lipids associated with dipalmitoylphosphatidylcholine (DPPC) or dimyristoylphosphatidylglycerol (DMPG) showed no anti-inflammatory activity, indicating that the release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity. The anti-inflammatory activity of cationic lipids was abrogated by the addition dipalmitoylphosphatidylethanolamine-poly(ethylene)glycol-2000 (DPPE-PEG(2000)) which blocks the interaction of cationic lipids with macrophages.

6 Because 6 Because of the significant role of protein kinase C (PKC) in the inflammatory process we have determined whether the cationic lipids used in this study inhibit PKC activity. The cationic lipids significantly inhibited the activity of PKC but not the activity of a non-related protein kinase, PKA. The synthesis of interleukin-6 (IL-6), which is not dependent on PKC activity for its induction in macrophages, was not modified in vitro or in situ by cationic lipids. The synthesis of NO and TNF-alpha in macrophages, both of which are PKC-dependent, was downregulated by cationic lipids.

7 These results demonstrate that cationic lipids can be considered as novel anti-inflammatory agents. The downregulation of pro-inflammatory mediators through interaction of cationic lipids with the PKC pathway may explain this anti-inflammatory activity. Furthermore, since cationic lipids have intrinsic anti-inflammatory activity, cationic liposomes should be used with caution to deliver nucleic acids for gene therapy in vivo.

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>>> Complete CA file indexing for chemical patents (or equivalents) <<<
>>> is included in file records.  A thesaurus is available for the  <<<
>>> USPTO Manual of Classifications in the /NCL, /INCL, and /RPCL   <<<
>>> fields.  This thesaurus includes catchword terms from the       <<<
>>> USPTO/MOC subject headings and subheadings.  Thesauri are also  <<<
>>> available for the WIPO International Patent Classification      <<<
>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4,     <<<
>>> /IC5, and /IC (/IC6) fields, respectively.  The thesauri in     <<<
>>> the /IC5 and /IC fields include the corresponding catchword     <<<
>>> terms from the IPC subject headings and subheadings.            <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


        126373 DC
          1075 DCS
        127180 DC
                  (DC OR DCS)
           417 CHOL
            11 DC CHOL
                  (DC(W)CHOL)
         14155 CHOLEST?
L18         11 L12(S) CHOLEST?

=> s l18 not l11

L19          9 L18 NOT L11

=> s l19 and (immuniz? or immunis? or adjuvant# or vaccin?)

          8205 IMMUNIZ?
           517 IMMUNIS?
         31146 ADJUVANT#
          7381 VACCIN?
L20          3 L19 AND (IMMUNIZ? OR IMMUNIS? OR ADJUVANT# OR VACCIN?)

=> d 1-3 bib abs; fil ca,caplus


L20  ANSWER 1 OF 3  USPATFULL
AN     97:75843  USPATFULL
TI     Lipid constructs for targeting to vascular smooth muscle tissue
IN     Male-Brune, Roxanne, Hillsborough, NC, United States
PA     California Institute of Technology, Pasadena, CA, United States
       (U.S. corporation)
PI     US 5660855  970826
AI     US 95-386579  950210 (8)
                        Searcher  :  Shears   308-4994
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DT Utility
EXNAM Primary Examiner: Jordan, Kimberly
LREP NeXstar Pharmaceuticals
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1110
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A lipid construct comprising an aminomannose derivatized cholesterol suitable for targeting smooth muscle cells and tissue. Preferred formulations contain 6-(cholest-5-en-3.beta.-yloxyl)hexyl-6-amino-6-deoxy-1-thio-.alpha.-D-mannopyranoside in liposome formulations wherein the formulations are delivered generally to arteries using percutaneous transluminal coronary angioplasty procedures. These formulations have applications in the reduction of restenosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 2 OF 3 USPATFULL
AN 97:73283 USPATFULL
TI Inducible nitric oxide synthase gene for treatment of disease
IN Billiar, Timothy R., Pittsburgh, PA, United States
Tzeng, Edith, Pittsburgh, PA, United States
Nussler, Andreas K., Neu-Ulm, Germany, Federal Republic of
Geller, David A., Pittsburgh, PA, United States
Simmons, Richard L., Pittsburgh, PA, United States
PA University of Pittsburgh of the Commonwealth System of Higher Education, Pittsburgh, PA, United States (U.S. corporation)
PI US 5658565 970819
AI US 94-265046 940624 (8)
DT Utility
EXNAM Primary Examiner: Low, Christopher S.F.
LREP Leydig, Voit & Mayer, Ltd.
CLMN Number of Claims: 40
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 2444
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention discloses a full-length human hepatocyte iNOS cDNA clone and various gene therapy applications utilizing an iNOS DNA sequence. In preferred embodiments of the disclosed invention, iNOS-directed gene therapy involves specific targeting of a DNA sequence encoding a protein or protein fragment with iNOS biological activity for treating vascular diseases and disorders, antitumor applications and in response to certain microbial infections.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 3 OF 3 USPATFULL
AN 94:59724 USPATFULL
TI Treatment of diseases by site-specific instillation of cells or site-specific transformation of cells and kits therefor
IN Nabel, Elizabeth G., Ann Arbor, MI, United States
Nabel, Gary J., Ann Arbor, MI, United States
PA The Regents of the University of Michigan, Ann Arbor, MI, United States (U.S. corporation)
PI US 5328470 940712
AI US 91-741244 910726 (7)
RLI Continuation-in-part of Ser. No. US 91-724509, filed on 28 Jun 1991 which is a continuation-in-part of Ser. No. US 89-331336, filed on 31 Mar 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Rosenbaum, C. Fred; Assistant Examiner: Alexander, V.
LREP Oblon, Spivak, McClelland, Maier & Neustadt
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1438
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the direct treatment towards the specific sites of a disease is disclosed. This method is based on the delivery of proteins by catheterization to discrete blood vessel segments using genetically modified or normal cells or other vector systems. Endothelial cells expressing recombinant therapeutic agent or diagnostic proteins are situated on the walls of the blood vessel or in the tissue perfused by the vessel in a patient. This technique, provides for the transfer of cells or vectors and expression of recombinant genes in vivo and allows the introduction of proteins of therapeutic or diagnostic value for the treatment of diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d que

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L21        2133 SEA CHOLESTER?(10A)(3(W)(BETA OR B))
L22          12 SEA L21 AND (IMMUNIZ? OR IMMUNIS? OR ADJUVANT# OR VACCIN
                ?)

=> s l22 not (l5 or l14)

L23          10 L22 NOT (L5 OR L14)

=> dup rem l23

PROCESSING COMPLETED FOR L23
L24           5 DUP REM L23 (5 DUPLICATES REMOVED)

=> d 1-5 .bevstr1


L24  ANSWER 1 OF 5  CA  COPYRIGHT 1997 ACS              DUPLICATE 1
AN   126:308676  CA
TI   Extracts of Ginkgo biloba leaves and Vaccinium myrtillus
     fruits prevent photo induced oxidation of low density lipoprotein
     cholesterol
AU   Francesca Rasetti, M.; Caruso, D.; Galli, G.; Bosisio, E.
CS   Faculty Pharmacy, University Milan, Milan, I-20133, Italy
SO   Phytomedicine (1997), 3(4), 335-338
     CODEN: PYTOEY; ISSN: 0944-7113
PB   Fischer
DT   Journal
LA   English
AB   G. biloba and V. myrtillus exts. inhibited dose-dependently the
     formation of cytotoxic oxysterol.  Protection against oxidn. was
     confirmed by partial restoration of normal electrophoretic mobility
     of low d. lipoprotein.  Therapeutic aspects on pathol. conditions
     due to free radicals including atherosclerosis were discussed.
IT   Natural products (pharmaceutical)
     RL: BOC (Biological occurrence); THU (Therapeutic use); BIOL
     (Biological study); OCCU (Occurrence); USES (Uses)
        (prevention of LDL cholesterol oxidn. by G. biloba and V.
        myrtillus exts.)
IT   Low-density lipoproteins
     RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL
     (Biological study); FORM (Formation, nonpreparative); OCCU
     (Occurrence)
        (prevention of LDL oxidn. by G. biloba and V. myrtillus exts.)
IT   Ginkgo biloba
        (prevention of LDL oxidn. by Gingko ext.)
IT   Vaccinium myrtillus
        (prevention of LDL oxidn. by Vaccinium ext.)
IT   566-27-8, 7.beta.-Hydroxycholesterol
```

RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(prevention of LDL cholesterol oxidn. by G. biloba and V. myrtillus exts.)

IT 566-26-7, Cholest-5-ene-**3.beta.**,7.alpha.-diol
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(prevention of LDL **cholesterol** oxidn. by G. biloba and V. myrtillus exts.)

IT 117-39-5, Quercetin
RL: BOC (Biological occurrence); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(prevention of LDL cholesterol oxidn. by quercetin)

L24 ANSWER 2 OF 5 CA COPYRIGHT 1997 ACS DUPLICATE 2
AN 125:165557 CA
TI Interaction of anti-cholesterol antibodies with human lipoproteins
AU Dijkstra, Jan; Swartz, Glann M, Jr.; Raney, Jennifer J.; Aniagolu, Jacinta; Toro, Luis; Nacy, Carol A.; Green, Shawn J.
CS EntreMed, Inc., Rockville, MD, 20850, USA
SO J. Immunol. (1996), 157(5), 2006-2013
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
AB Inoculation of mice with cholesterol-rich liposomes contg. the **adjuvant** monophosphoryl lipid A results in the prodn. of antiserum contg. IgM to cholesterol. The specificity of the Ab was to **cholesterol** and structurally similar sterols contg. a **3.beta.**-hydroxyl group. Anti-**cholesterol** binding activity was significantly diminished if the **3.beta.**-hydroxyl was altered by either epimerization, substitution, oxidn., or esterification. A similar specificity for **3.beta.**-hydroxy-sterols was obsd. for an anti-**cholesterol** IgM mAb. Both hyperimmune serum and the mAb reacted with intact human very-low-/intermediate-d. lipoprotein (VLDL/IDL) and low-d. lipoproteins (LDL), but not high-d. lipoproteins (HDL), in an ELISA, but could react with total lipid exts. contg. cholesterol that were prepd. from all three lipoprotein classes. Functionally, immune serum or the mAb aggregated and induced a fusion-like reaction with VLDL/IDL and LDL at low temps.: these aggregates result in spherical structures visible with light microscopy. Similarly, binding of anti-cholesterol Ab to small cholesterol-rich liposomes resulted in the appearance of vesicular structures with approx. 20- to 200-fold increased diams. These data demonstrate that the anti-cholesterol Ab recognize unesterified cholesterol in VLDL/IDL and IDL; high-d. lipoprotein cholesterol in the intact lipoprotein, however, appears to be protected from reaction with these Ab.

IT Immunoglobulins

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(M, interaction of anti-cholesterol antibodies with human lipoproteins)

IT Arteriosclerosis
(atherosclerosis, interaction of anti-cholesterol antibodies with human lipoproteins in relation to)

IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(intermediate-d., interaction of anti-cholesterol antibodies with human lipoproteins)

IT Glycophospholipids
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(lipid A, **adjuvant**; interaction of anti-cholesterol antibodies with human lipoproteins)

IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(low-d., interaction of anti-cholesterol antibodies with human lipoproteins)

IT Antibodies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(monoclonal, interaction of anti-cholesterol antibodies with human lipoproteins)

IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(very-low-d., interaction of anti-cholesterol antibodies with human lipoproteins)

IT 57-88-5, Cholesterol, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(interaction of anti-cholesterol antibodies with human lipoproteins)

L24 ANSWER 3 OF 5 CA COPYRIGHT 1997 ACS DUPLICATE 3
AN 117:205483 CA
TI Maintenance or stimulation of steroidogenic enzymes and testosterone production in rat Leydig cells by continuous and pulsatile infusions of luteinizing hormone during passive **immunization** against gonadotropin-releasing hormone
AU Chase, D. J.; Karle, J. A.; Fogg, R. E.
CS Dep. Biol. Sci., State Univ. New York, Binghamton, NY, 13902-6000, USA
SO J. Reprod. Fertil. (1992), 95(3), 657-67
CODEN: JRPFA4; ISSN: 0022-4251

DT Journal
LA English
AB The importance of the pulsatility of LH secretion in maintaining key enzymes in the testosterone biosynthetic pathway in Leydig cells was studied using rats in which LH secretion was suppressed by passive **immunization** against gonadotropin-releasing hormone (GnRH) and replaced by continuous or pulsatile i.v. infusions of exogenous LH (all delivering the same daily dose of the hormone). Continuous infusions (12.5 ng/100 g/h) were compared with infusions of 1 min pulses every 2 h (25 ng/100 g) and every 4 h (50 ng/100 g). After 5 days of treatment in vivo with sheep anti-GnRH serum (or normal sheep serum) and with LH (or vehicle), Leydig cells were purified and assayed in vitro for max. prodn. of testosterone stimulated by human chorionic gonadotropin (hCG) or supported by 25-hydroxycholesterol and for the activities of **cholesterol** side-chain cleavage, .DELTA.5-**3.beta**.-hydroxysteroid dehydrogenase-.DELTA.5-4-isomerase (3.beta.-HSD-isomerase), and 17.alpha.-hydroxylase. Activity of 3.beta.-HSD-isomerase was reduced by about 40% by anti-GnRH treatment and was increased by all LH regimens in anti-GnRH-treated animals, with no consistent pattern in the effects of the different LH regimens. Results for testosterone-producing capacity and the other two enzymes differed in several respects. Treatment with anti-GnRH serum markedly reduced basal, hCG-stimulated, and 25-hydroxycholesterol-supported testosterone prodn. (by 80-90%) and the activities of cholesterol side-chain cleavage (about 80%) and 17.alpha.-hydroxylase (about 65%). Infusion of exogenous LH in any of the regimens tested prevented these changes or increased the activities to values greater than those in normal serum-treated controls. There was a consistent trend in the effects of LH replacement regimens on these parameters of steroidogenic activity: continuous infusions were more effective than pulses at 2-h intervals, and these in turn were more effective than pulses at 4-h intervals, suggesting that the frequency of LH exposure is more important than the amplitude of individual exposures in maintaining Leydig cell steroidogenic function. Consistent differences among groups in hCG-stimulated relative to 25-hydroxycholesterol-supported testosterone prodn. suggest that some constituents of Leydig cells prior to cholesterol side-chain cleavage enzyme are more sensitive to LH withdrawal and deviations from optimal LH exposure than are the side-chain cleavage and subsequent enzymes in the testosterone biosynthetic pathway.
IT Testis, composition
(Leydig cell, steroidogenic enzymes of and testosterone formation by, LH effect on)
IT Enzymes
RL: BIOL (Biological study)
(steroid-forming, of testis Leydig cell, LH effect on)
IT 58-22-0, Testosterone

RL: FORM (Formation, nonpreparative)
(formation of, by testis Leydig cell, LH effect on)

IT 9029-67-8, Steroid 17.alpha.-hydroxylase 9031-36-1 37292-81-2, Cholesterol side-chain-cleaving enzyme
RL: BIOL (Biological study)
(of testis Leydig cell, LH effect on)

IT 9044-85-3, .DELTA.5-3.beta.-Hydroxy steroid dehydrogenase
RL: BIOL (Biological study)
(of testis, LH effect on)

IT 9002-67-9, LH
RL: BIOL (Biological study)
(steroid formation by testis Leydig cells response to)

L24 ANSWER 4 OF 5 CA COPYRIGHT 1997 ACS DUPLICATE 4
AN 117:187206 CA
TI Expansion of the mammalian **3.beta**.-hydroxysteroid dehydrogenase/plant dihydroflavonol reductase superfamily to include a bacterial **cholesterol** dehydrogenase, a bacterial UDP-galactose-4-epimerase, and open reading frames in **vaccinia** virus and fish lymphocystis disease virus
AU Baker, Michael E.; Blasco, Rafael
CS Dep. Med. 0623B, Univ. California, San Diego, La Jolla, CA, 92093-0623, USA
SO FEBS Lett. (1992), 301(1), 89-93
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
AB Mammalian 3.beta.-hydroxysteroid dehydrogenase and plant dihydroflavonol reductases are descended from a common ancestor. Here, evidence is presented that Nocardia cholesterol dehydrogenase, Escherichia coli UDP-galactose-4-epimerase, and open reading frames (ORFs) in **vaccinia** virus and fish lymphocystis disease virus are homologous to 3.beta.-hydroxysteroid dehydrogenase and dihydroflavonol reductase. Anal. of a multiple alignment of these sequences indicates that viral ORFs are most closely related to the mammalian 3.beta.-hydroxysteroid dehydrogenases. The ancestral protein of this superfamily is likely to be one that metabolized sugar nucleotides. The sequence similarity between 3.beta.-hydroxysteroid dehydrogenase and the viral ORFs is sufficient to suggest that these ORFs have an activity that is similar to **3.beta**.-hydroxysteroid dehydrogenase or **cholesterol** dehydrogenase, although the putative substrates are not yet known.

IT Escherichia coli
(UDP-galactose epimerase of, sequence homol. of, with hydroxysteroid dehydrogenase/dihydroflavonol reductase superfamily)

IT Nocardia

(cholesterol dehydrogenase of, sequence homol. of, with hydroxysteroid dehydrogenase/dihydroflavonol reductase superfamily)

IT Protein sequences
(of dihydroflavonol reductase/hydroxysteroid dehydrogenase superfamily, of mammals and bacteria and viruses, homologies among)

IT Evolution
(divergent, of dihydroflavonol reductase/hydroxysteroid dehydrogenase superfamily)

IT Virus, animal
(lymphocystis disease of fish, hydroxysteroid dehydrogenase-like enzyme encoded by ORF of, sequence homol. of, with dihydroflavonal reductase/hydroxysteroid dehydrogenase superfamily)

IT Virus, animal
(**vaccinia**, hydroxysteroid dehydrogenase-like enzyme encoded by ORF of, sequence homol. of, with dihydroflavonal reductase/hydroxysteroid dehydrogenase superfamily)

IT 143927-70-2
RL: BIOL (Biological study)
(ORF-encoded, of fish lymphocytis disease virus, sequence homol. of, with hydroxysteroid dehydrogenase/dihydroflavonol reductase superfamily)

IT 143927-65-5
RL: BIOL (Biological study)
(ORF-encoded, of **vaccinia** virus, sequence homol. of, with hydroxysteroid dehydrogenase/dihydroflavonol reductase superfamily)

IT 98743-49-8
RL: BIOL (Biological study)
(evolution and sequence homologies of enzyme superfamily contg.)

IT 9032-89-7, UDP-galactose-4-epimerase
RL: BIOL (Biological study)
(sequence homol. of, of Escherichia coli, with dihydroflavonol reductase/hydroxysteroid dehydrogenase superfamily)

IT 67775-34-2, Cholesterol dehydrogenase
RL: BIOL (Biological study)
(sequence homol. of, of Nocardia, with dihydroflavonol reductase/hydroxysteroid dehydrogenase superfamily)

L24 ANSWER 5 OF 5 CA COPYRIGHT 1997 ACS DUPLICATE 5
AN 70:9183 CA
TI Clinical experiences with aminoglutethimide (Elipten), a new inhibitor of steroid biosynthesis in the adrenal
AU Horky, K.; Kuechel, Otto; Gregorova, Inge; Jirankova, J.; Matys, Zdenek
CS III. Med. Klin., Karlova Univ., Prague, Czech.
SO Schweiz. Med. Wochenschr. (1968), 98(47), 1843-51

CODEN: SMWOAS
DT Journal
LA German
AB Aminoglutethimide (I), which inhibits steroid synthesis by blocking the conversion of **cholesterol** to **3.beta**.-hydroxypregn-5-en-20-one, was studied in 36 patients with various adrenal gland disorders. The best results during I therapy were observed in autonomous hypercortisolism of the Cushing type in patients with adenoma or adrenal carcinoma. Protein breakdown and electrolyte disturbances were improved in presurgical patients by conservative therapy with I, improving the surgical prognosis. I administration to patients with ACTH-dependent Cushing's syndrome was less effective. Good results were also observed in patients with hyperaldosteronism secondary to idiopathic edema, with ascitic cirrhosis of the liver, and with renal-vascular or severe essential hypertension. I exhibited marked saluretic and diuretic effects in edema and was an effective hypotensive **adjuvant** drug in patients with severe hypertension.
IT Diuretics
(aminoglutethimide as)
IT Cirrhosis
Hypertension
Adrenal cortex, diseases or disorders
(aminoglutethimide in treatment of)
IT Salivary glands
(aminoglutethimide stimulation of secretion by)
IT 125-84-8
RL: BIOL (Biological study)
(in adrenocortical disorder treatment)

=> fil
biosi,medl,embas,lifesci,biotechd,wpid,confsci,dissabs,scisearch,jicst,promt,toxlit,toxlin,drugu,drugb,drugnl,druglaunch

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=> s l22

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   5 FILES SEARCHED...
   6 FILES SEARCHED...
  12 FILES SEARCHED...
L25          11 L22

=> s l25 not (l8 or l17)

L26          11 L25 NOT (L8 OR L17)

=> dup rem l26

DUPLICATE IS NOT AVAILABLE IN 'DRUGLAUNCH'.
                        Searcher  :  Shears   308-4994
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ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L26
L27 3 DUP REM L26 (8 DUPLICATES REMOVED)

=> d 1-3 bib abs; fil uspat; s l22

L27 ANSWER 1 OF 3 MEDLINE DUPLICATE 1
AN 96355004 MEDLINE
TI Interaction of anti-cholesterol antibodies with human lipoproteins.
AU Dijkstra J; Swartz G M Jr; Raney J J; Aniagolu J; Toro L; Nacy C A; Green S J
CS EntreMed, Inc., Rockville, MD 20850, USA.
SO JOURNAL OF IMMUNOLOGY, (1996 Sep 1) 157 (5) 2006-13.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 9701
EW 19970104
AB Inoculation of mice with cholesterol-rich liposomes containing the **adjuvant** monophosphoryl lipid A results in the production of antiserum containing IgM Ab to cholesterol. The specificity of the Ab was to **cholesterol** and structurally similar sterols containing a **3 beta**-hydroxyl group. Anti-**cholesterol** binding activity was significantly diminished if the **3 beta**-hydroxyl was altered by either epimerization, substitution, oxidation, or esterification. A similar specificity for **3 beta**-hydroxy-sterols was observed for an anti-**cholesterol** IgM mAb. Both hyperimmune serum and the mAb reacted with intact human very-low-/intermediate-density lipoprotein (VLDL/IDL) and low-density lipoproteins (LDL), but not high-density lipoproteins (HDL), in an ELISA, but could react with total lipid extracts containing cholesterol that were prepared from all three lipoprotein classes. Functionally, immune serum or the mAb aggregated and induced a fusion-like reaction with VLDL/IDL and LDL at low temperatures: these aggregates result in spherical structures visible with light microscopy. Similarly, binding of anti-cholesterol A to small cholesterol-rich liposomes resulted in the appearance of vesicular structures with approximately 20- to 200-fold increased diameters. These data demonstrate that the anti-cholesterol Ab recognize unesterified cholesterol in VLDL/IDL and LDL; high-density lipoprotein cholesterol in the intact lipoprotein, however, appears to be protected from reaction with these Ab.

L27 ANSWER 2 OF 3 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 2
AN 92:522350 BIOSIS

DN BA94:130425

TI MAINTENANCE OR STIMULATION OF STEROIDOGENIC ENZYMES AND TESTOSTERONE PRODUCTION IN RAT LEYDIG CELLS BY CONTINUOUS AND PULSATILE INFUSIONS OF LUTEINIZING HORMONE DURING PASSIVE **IMMUNIZATION** AGAINST GONADOTROPHIN-RELEASING HORMONE.

AU CHASE D J; KARLE J A; FOGG R E

CS DEP. BIOLOGICAL SCIENCES, STATE UNIV. NEW YORK, BINGHAMTON, N.Y. 13902-6000, USA.

SO J REPROD FERTIL 95 (3). 1992. 657-667. CODEN: JRPFA4 ISSN: 0022-4251

LA English

AB The importance of the pulsatility of luteinizing hormone (LH) secretion in maintaining key enzymes in the testosterone biosynthetic pathway in Leydig cells was studied using rats in which LH secretion was suppressed by passive **immunization** against gonadotrophin-releasing hormone (GnRH) and replaced by continuous or pulsatile i.v. infusion of exogenous LH, all delivering the same daily dose of the hormone (300 ng per 100 g NIDDK-ovine LH-24). Continuous infusions (12.5 ng per 100 g h-1) were compared with infusions of 1 min pulses every 2 h (25 ng per 100 g) and every 4 h (50 ng per 100 g). After 5 days of treatment in vivo with sheep anti-GnRH serum (or normal sheep serum) and LH (or vehicle), Leydig cells were purified and assayed in vitro for maximum production of testosterone stimulated by human chorionic gonadotrophin (hCG) and supported by 25-hydroxycholesterol and for the activities of **cholesterol** side-chain cleavage, .DELTA.5-**3**.**beta**.-hydroxysteroid dehydrogenase-.DELTA.5-4-isomerase (**3**.**beta**.-HSD-isomerase) and 17.alpha.-hydroxylase. Relative contents of **cholesterol** side-chain cleavage and 17.alpha.-hydroxylase were also quantified by western and immunoblotting analysis. Activity of 3.beta.-HSD-isomerase was reduced by about 40% by anti-GnRH treatment and was increased by all LH regimens in anti-GnRH-treated animals, with no consistent pattern in the effects of the different LH regimens. Results for testosterone-producing capacity and the other two enzymes differed in several respects. Treatment with anti-GnRH serum markedly reduced basal, hCG-stimulated and 25-hydroxycholesterol-supported testosterone production (by 80-90%) and the activities of cholesterol side-chain cleavage (about 80%) and 17.alpha.-hydroxylase (about 65%). Infusion of exogenous LH in any of the regimens tested prevented these changes or increased the activities to values greater than those in normal serum-treated controls. Differences in immunodetectable contents of the two enzymes generally paralleled those in enzyme activities. There was a consistent trend in the effects of LH replacement regimens on these parameters of steroidogenic activity: continuous infusions were more effective than pulses at 2 h intervals and these in turn were more effective than pulses at 4 h intervals, suggesting that the frequency of LH exposure is more important than the amplitude of individual exposures in maintaining Leydig cell steroidogenic function. Consistent

differences among groups in hCG-stimulated relative to 25-hydroxycholesterol-supported testosterone production suggest that some constituents of Leydig cells prior to cholesterol side-chain cleavage enzyme are more sensitive to LH withdrawal and deviations from 'optimal' LH exposure than are the side-chain cleavage and subsequent enzymes in the testosterone biosynthetic pathway.

L27 ANSWER 3 OF 3 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 3
AN 92:322624 BIOSIS
DN BA94:24465
TI EXPANSION OF THE MAMMALIAN **3-BETA** HYDROXYSTEROID DEHYDROGENASE PLANT DIHYDROFLAVONOL REDUCTASE SUPERFAMILY TO INCLUDE A BACTERIAL **CHOLESTEROL** DEHYDROGENASE A BACTERIAL UDP-GALACTOSE-4-EPIMERASE AND OPEN READING FRAMES IN **VACCINIA** VIRUS AND FISH LYMPHOCYSTIS DISEASE VIRUS.
AU BAKER M E; BLASCO R
CS DEP. MED., 0623B, UNIV. CALIFORNIA, SAN DIEGO, 9500 GILMAN DRIVE, LA JOLLA, CALIF. 92093-0623, USA.
SO FEBS (FED EUR BIOCHEM SOC) LETT 301 (1). 1992. 89-93. CODEN: FEBLAL ISSN: 0014-5793
LA English
AB Mammalian 3.beta.-hydroxysteroid dehydrogenase and plant dihydroflavonol reductases are descended from a common ancestor. Here we present evidence that Nocardia cholesterol dehydrogenase, Escherichia coli UDP-galactose-4 epimerase, and open reading frames in **vaccinia** virus and fish lymphocystis disease virus are homologous to 3.beta.-hydroxysteroid dehydrogenase and dihydroflavonol reductase. Analysis of a multiple alignment of these sequences indicates that viral ORFs are most closely related to the mammalian 3.beta.-hydroxysteroid dehydrogenases. The ancestral protein of this superfamily is likely to be one that metabolized sugar nucleotides. The sequence similarity between 3.beta.-hydroxysteroid dehydrogenase and the viral ORFs is sufficient to suggest that these ORFs have an activity that is similar to **3.beta.**-hydroxysteroid dehydrogenase or **cholesterol** dehydrogenase, although the putative substrates are not yet known.

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 9 Dec 1997 (19971209/PD)
FILE LAST UPDATED: 10 Dec 1997 (971210/ED)
HIGHEST PATENT NUMBER: US5697097
CA INDEXING IS CURRENT THROUGH 10 Dec 1997 (971210/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 9 Dec 1997 (19971209/PD)
REVISED CLASS FIELDS (/NCL) CURRENT THROUGH: AUG 1997
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: JUN 1997
Searcher : Shears 308-4994

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>>> fields.  This thesaurus includes catchword terms from the       <<<
>>> USPTO/MOC subject headings and subheadings.  Thesauri are also  <<<
>>> available for the WIPO International Patent Classification      <<<
>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4,     <<<
>>> /IC5, and /IC (/IC6) fields, respectively.  The thesauri in     <<<
>>> the /IC5 and /IC fields include the corresponding catchword     <<<
>>> terms from the IPC subject headings and subheadings.            <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


         13667 CHOLESTER?
       2208423 3
        160616 BETA
           377 BETAS
        160693 BETA
                  (BETA OR BETAS)
       1098828 B
           133 CHOLESTER?(10A)(3(W)(BETA OR B))
          8205 IMMUNIZ?
           517 IMMUNIS?
         31146 ADJUVANT#
          7381 VACCIN?
L28         19 L21 AND (IMMUNIZ? OR IMMUNIS? OR ADJUVANT# OR VACCIN?)

=> s l28 not (l11 or l20)

L29         16 L28 NOT (L11 OR L20)

=> d 1-16 bib abs; fil hom


L29  ANSWER 1 OF 16  USPATFULL
AN     97:112593  USPATFULL
TI     Glycoside derivatives of acetaminophen
IN     Klemke, R. -Erich, Hilzingen, Germany, Federal Republic of
       Koreeda, Masato, Ann Arbor, MI, United States
       Houston, Todd A., Timonium, MD, United States
       Shull, Brian K., Ann Arbor, MI, United States
                        Searcher  :  Shears   308-4994
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Tuinman, Roeland J., Fenton, MI, United States
PA Harrier Inc., Hermosa Beach, CA, United States (U.S. corporation)
PI US 5693767 971202
AI US 94-251869 940601 (8)
RLI Continuation-in-part of Ser. No. US 93-6447, filed on 21 Jan 1993, now abandoned which is a continuation-in-part of Ser. No. US 92-815691, filed on 24 Jan 1992, now abandoned which is a continuation-in-part of Ser. No. US 91-733915, filed on 22 Jul 1991, now abandoned which is a continuation-in-part of Ser. No. US 91-644002, filed on 22 Jan 1991, now patented, Pat. No. US 5278296, issued on 11 Jan 1994
DT Utility
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Lee, Howard C.
LREP Medlen & Carroll, LLP
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 1043
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel glycosides, especially steroidal and non-steroidal glycosides are provided. The steroidal and non-steroidal glycosides preferably are prepared from aglycons which possess valuable properties such as pharmacological properties. The glycosides are prepared from useful aglycons and possess useful properties which are the same as those of their respective unglycosylated aglycons. The glycosides are provided in acylated and deacylated form. The acylated glycosides after hydrolysis of the acyl groups possess enhanced water solubility properties, as illustrated in the case where the aglycon is acetominophen.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 2 OF 16 USPATFULL
AN 96:116123 USPATFULL
TI Method of preparing gas and gaseous precursor-filled microspheres
IN Unger, Evan C., Tucson, AZ, United States
Fritz, Thomas A., Tucson, AZ, United States
Matsunaga, Terry, Tucson, AZ, United States
Ramaswami, VaradaRajan, Tucson, AZ, United States
Yellowhair, David, Tucson, AZ, United States
Wu, Guanli, Tucson, AZ, United States
PA ImaRx Pharmaceutical Corp., Tucson, AZ, United States (U.S. corporation)
PI US 5585112 961217
AI US 93-159687 931130 (8)
RLI Continuation-in-part of Ser. No. US 93-160232, filed on 30 Nov 1993, now abandoned And a continuation-in-part of Ser. No. US 93-159674, filed on 30 Nov 1993, now abandoned , each Ser. No. US - which is a continuation-in-part of Ser. No. US 93-76239, filed

on 11 Jun 1993, now patented, Pat. No. US 5469854 which is a continuation-in-part of Ser. No. US 91-717084, filed on 18 Jun 1991, now patented, Pat. No. US 5228446 And Ser. No. US 91-716899, filed on 18 Jun 1991, now abandoned which is a continuation-in-part of Ser. No. US 90-569828, filed on 20 Aug 1990, now patented, Pat. No. US 5088499 which is a continuation-in-part of Ser. No. US 89-455707, filed on 22 Dec 1989, now abandoned , said Ser. No. US -717084 which is a continuation-in-part of Ser. No. US 90-569828, filed on 20 Aug 1990, now patented, Pat. No. US 5088499

DT Utility
EXNAM Primary Examiner: Kishore, Gollamudi S.
LREP Woodcock Washburn Kurtz Mackiewicz & Norris
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 3161
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of and apparatus for preparing temperature activated gaseous precursor-filled liposomes are described. Gaseous precursor-filled liposomes prepared by these methods are particularly useful, for example, in ultrasonic imaging applications and in therapeutic drug delivery systems.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 3 OF 16 USPATFULL
AN 96:19079 USPATFULL
TI Glycoside compounds and production and use thereof
IN Klemke, R. Erich, D-78247 Hilzingen, Germany, Federal Republic of
PA Klemke, R. Erich, Germany, Federal Republic of (non-U.S. individual)
PI US 5496806 960305
AI US 94-239373 940506 (8)
RLI Division of Ser. No. US 93-6447, filed on 21 Jan 1993, now abandoned which is a continuation-in-part of Ser. No. US 92-815691, filed on 24 Jan 1992, now abandoned which is a continuation-in-part of Ser. No. US 91-733915, filed on 22 Jul 1991, now abandoned which is a continuation-in-part of Ser. No. US 91-644002, filed on 22 Jan 1991, now patented, Pat. No. US 5278296
PRAI DE 90-4001895 900123
DT Utility
EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Lee, Howard C.
LREP Young, MacFarlane & Wood
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 412

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel glycosides 7-ketosteryl di-O-acyl-pyranoside and 7-.beta.-hydroxycholesteryl 2,3-dideoxy-.alpha.-D-erythro-hex-2-enopyranoside. The glycosides possess valuable pharmacological properties as a medicament. In particular, the cholesterol glycoside in vivo exhibits a selective cell-destructive activity on malignant cells which activity is substantially free of side effects on normal cells. The glycosides possess useful properties, especially pharmacological properties which are the same as the respective unglycosylated aglycon.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 4 OF 16 USPATFULL

AN 95:99184 USPATFULL

TI Aromatic nitro and nitroso compounds and their metabolites useful as anti-viral and anti-tumor agents

IN Kun, Ernest, Mill Valley, CA, United States
Mendeleyev, Jerome, San Francisco, CA, United States
Kirsten, Eva, Daly City, CA, United States

PA Octamer, Inc., Sausalito, CA, United States (U.S. corporation)

PI US 5464871 951107

AI US 93-76313 930611 (8)

RLI Continuation-in-part of Ser. No. US 93-60409, filed on 12 May 1993

DT Utility

EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Mach, D. Margaret M.

LREP Halluin, Albert P.Pennie & Edmonds

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 4 Drawing Page(s)

LN.CNT 906

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Unsubstituted or substituted halo nitro and nitroso compounds and their metabolites are potent, selective and non-toxic inhibitors and supressants of cancer growth and viral infections in a mammalian host. The compounds are particularly useful for treatment and supression of tumors and viruses associated with breast cancer, AIDS, herpetic episodes and cytomegaloviral infections. The methods of treatment of tumorigenic and viral diseases by halo nitro nitroso compounds and their metabolites are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 5 OF 16 USPATFULL

AN 94:3918 USPATFULL

TI Production of hydroxysteryl glycoside compounds

IN Klemke, R.-Erich, Hilzingen, Germany, Federal Republic of

PA Gelman Sciences Inc., Ann Arbor, MI, United States (U.S. corporation)
PI US 5278296 940111
AI US 91-644002 910122 (7)
PRAI DE 90-4001895 900123
DT Utility
EXNAM Primary Examiner: Husarik, Nancy S.
LREP Krass & Young
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 504
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel glycosides, especially steroidal glycosides, and a novel method of their production, are provided. For the novel method of producing novel glycosides, hydroxysteryl compounds are glycosylated with tri-O-acyl glucal using molecular iodine as a reaction catalyst. In this method an alcohol or phenol, especially a hydroxy-steroid such as a water-insoluble cholesterol, is glycosylated, such that the glycosylation is performed in a single step. The resulting steryl pyranoside is by oxidation converted to the corresponding 7-ketosteryl di-O-acyl-pyranoside. The latter pyranoside is selectively reduced to provide the corresponding 7-.beta.-hydroxysteryl 2,3-dideoxy-.alpha.-D-erythro-hex-2-enopyranoside. The steroidal glycosides obtained in this way possess valuable pharmacological properties. In particular, the glycosides in vivo exhibit a selective cell-destructive activity on malignant cells which activity is substantially free of side effects on normal cells. The glycosides also possess a drive-enhancing (stimulating) activity and an anti-inflammatory (immunosuppressive or immunoregulatory) activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 6 OF 16 USPATFULL
AN 91:42708 USPATFULL
TI Steroidal glycolipids as host resistance stimulators against viral infection
IN Durette, Philippe L., New Providence, NJ, United States
Hagmann, William K., Westfield, NJ, United States
Ponpipom, Mitree M., Branchburg, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5019568 910528
AI US 89-370058 890621 (7)
DCD 20071113
RLI Continuation of Ser. No. US 87-63197, filed on 18 Jun 1987, now abandoned
DT Utility
EXNAM Primary Examiner: Friedman, Stanley J.; Assistant Examiner:
Searcher : Shears 308-4994

Criares, Theodore J.
LREP Harbour, John W.; Pfeiffer, Hesna J.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1174
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are pharmaceutical compositions for enhancing human host resistance against opportunistic infection in an individual immunocompromised by an AIDS-related virus, consisting essentially of an anti-viral, anti-AIDS drug selected from the group consisting of ansamycin, ribavirin, dideoxycitidine, HPA-23, AL-721, foscarnet, and azidothymidine and a glycolipid compound consisting essentially of the formula: ##STR1## where: R.sup.1 is .alpha. or .beta.-D-1-thiomannopyranoside, .alpha. or .beta.-L-1-thiofucopyranoside.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 7 OF 16 USPATFULL
AN 90:87331 USPATFULL
TI Steroidal glycolipids as host resistance stimulators against viral infection
IN Durette, Philippe L., New Providence, NJ, United States
Hagmann, William K., Westfield, NJ, United States
Ponpipom, Mitree M., Branchburg, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 4970199 901113
AI US 89-378424 890710 (7)
RLI Continuation of Ser. No. US 87-63000, filed on 18 Jun 1987, now abandoned
DT Utility
EXNAM Primary Examiner: Griffin, Ronald W.; Assistant Examiner: Carson, Nancy S.
LREP Harbour, John W.; North, Robert J.; Pfeiffer, Hesna J.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1189
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are steroidal derivatives of glycolipids, in which steroids are bridged, via a medium length hydrocarbon chain, to 1-thio-D-mannopyranoses or 1-thio-L-fucopyranoses in combination with an anti-AIDS drug, that protect an immunocomprimised hot, particularly resulting from an AIDS-related virus, against opportunistic infection.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 8 OF 16 USPATFULL
AN 90:56217 USPATFULL
TI Steroidal glycolipids as host resistance stimulators against viral infection
IN Durette, Philippe L., New Providence, NJ, United States
Ponpipom, Mitree M., Branchburg, NJ, United States
Hagmann, William K., Westfield, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 4942154 900717
AI US 87-62997 870618 (7)
DCD 20040324
DT Utility
EXNAM Primary Examiner: Griffin, Ronald W.; Assistant Examiner: Carson, Nancy S.
LREP Harbour, John W.; North, Robert J.; Pfeiffer, Hesna J.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1176
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are steroidal derivatives of glycolipids, in which steroids are bridged, via a medium length hydrocarbon chain, to 1-thio-D-mannopyranoses or 1-thio-L-fucopyranoses that protect an immunocompromised host, particularly resulting from an AIDS-related virus, against opportunistic infection.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 9 OF 16 USPATFULL
AN 87:20717 USPATFULL
TI Steroidal glycolipids
IN Hagmann, William K., Westfield, NJ, United States
Ponpipom, Mitree M., Branchburg, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 4652637 870324
AI US 85-801905 851125 (6)
DT Utility
EXNAM Primary Examiner: Brown, Johnnie R.; Assistant Examiner: Peselev, Elli
LREP North, Robert J.; Speer, Raymond M.; Pfeiffer, Hesna J.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Described are derivatives of glycolipids with substituted steroids bridged via a medium length hydrocarbon chain to 1-thio-D-mannopyranoses or 1-thio-L-fucopyranoses. These compounds protect an immunocompromised human or animal host against

opportunistic infection by virtue of their immunostimulant properties.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 10 OF 16 USPATFULL
AN 87:20633 USPATFULL
TI Steroidal glycolipids as host resistance stimulators
IN Hagmann, William K., Westfield, NJ, United States
Durette, Philippe L., New Providence, NJ, United States
Ponpipom, Mitree M., Branchburg, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 4652553 870324
AI US 85-801906 851125 (6)
DT Utility
EXNAM Primary Examiner: Brown, Johnnie R.
LREP North, Robert J.; Speer, Raymond M.; Pfeiffer, Hesna J.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1,9
DRWN No Drawings
LN.CNT 839
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Described are derivatives of glycolipids with substituted steroids bridged via a medium length hydrocarbon chain to 1-thio-D-mannopyranoses or 1-thio-L-fucopyranoses. These compounds protect an immunocompromised human or animal host against opportunistic infection by virtue of their immunostimulant properties.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 11 OF 16 USPATFULL
AN 87:20485 USPATFULL
TI Synthesis of 1.alpha.,25-dihydroxy-24R-fluorocholecalciferol and 1.alpha.,25-dihydroxy-24S-fluorocholecalciferol
IN Partridge, John J., Upper Montclair, NJ, United States
Shiuey, Shian-Jan, Nutley, NJ, United States
Uskokovic, Milan R., Upper Montclair, NJ, United States
PA Hoffman-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 4652405 870324
AI US 82-405854 820806 (6)
RLI Continuation-in-part of Ser. No. US 81-297446, filed on 28 Aug 1981, now abandoned
DT Utility
EXNAM Primary Examiner: Roberts, Elbert L.
LREP Saxe, Jon S.; Leon, Bernard S.; Boxer, Mathew
CLMN Number of Claims: 47
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 1215
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB 1.alpha.,25-Dihydroxy-24R-fluorocholecalciferol and 1.alpha.,25-dihydroxy-24S-fluorocholecalciferol, analogs of 1.alpha.,25-dihydroxy-cholecalciferol which is physiologically the most active metabolite of vitamin D.sub.3, are synthesized in a multistep process from the known substance 1.alpha.,3.beta.-dihydroxyandrost-5-en-17-one. The new analogs are characterized by the ability to increase intestinal calcium transport, increase serum calcium and phosphate concentrations and to increase the deposition of these minerals in bones. These compounds will find a ready application as substitutes for natural 1.alpha.,25-dihydroxycholecalciferol in the treatment of disease states characterized by metabolic calcium and phosphate deficiencies. Exemplary of such disease states are the following: osteosclerosis, anticonvulsant treatment, osteopenia, fibrogenesis-imperfecta ossium, secondary hyperparathyrodism, hypoparathyroidism, hyperparathyroidism, cirrhosis, obstructive jaundice, drug induced metabolism, medullary carcinoma, chronic renal disease, hypophosphatemic VDRR, vitamin D-dependent rickets, sarcoidosis, glucocorticoid antagonism, malabsorption syndrome, steatorrhea, tropical sprue, idiopathic hypercalcemia and milk fever.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 12 OF 16 USPATFULL
AN 87:6433 USPATFULL
TI Method for the immunoanalysis of cholesterol epoxides
IN Schaffner, Carl P., 10 Youngs Rd., Trenton, NJ, United States 08619
PI US 4639420 870127
AI US 84-673768 841121 (6)
DT Utility
EXNAM Primary Examiner: Nucker, Christine M.; Assistant Examiner: DeSantis, Patricia L.
LREP Flehr, Hohbach, Test, Albritton & Herbert
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1301
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An immunoassay is provided for cholesterol epoxide. To prepare the antibodies used in the immunoassay, novel immunogens, are prepared which comprise a 3,5(6)-transdiaxial-dihydroxycholestane-6(5)-yl-hapten adduct linked to a covalently bonded bridge to a carrier protein. To detect cholesterol epoxide in the sample, it is converted to the hapten adduct, then contacted with the selected

antibody.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 13 OF 16 USPATFULL
AN 87:1313 USPATFULL
TI Synthesis of 1.alpha.,25-dihydroxy-24R-fluorocholecalciferol and 1.alpha.,25-dihydroxy-24S-fluorocholecalciferol
IN Partridge, John J., Upper Montclair, NJ, United States
Shiuey, Shian-Jan, Nutley, NJ, United States
Uskokovic, Milan R., Upper Montclair, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 4634692 870106
AI US 84-599086 840411 (6)
RLI Continuation-in-part of Ser. No. US 82-405854, filed on 6 Aug 1982 which is a continuation-in-part of Ser. No. US 81-297446, filed on 28 Aug 1981, now abandoned
DT Utility
EXNAM Primary Examiner: Schenkman, Leonard; Assistant Examiner: Lipovsky, Joseph A.
LREP Saxe, Jon S.; Leon, Bernard S.; Boxer, Matthew
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1182
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB 1.alpha.,25-Dihydroxy-24R-fluorocholecalciferol and 1.alpha.,25-dihydroxy-24S-fluorocholecalciferol, analogs of 1.alpha.,25-dihydroxy-cholecalciferol which is physiologically the most active metabolite of vitamin D.sub.3, are synthesized in a multistep process from the known substance 1.alpha.,3.beta.-dihydroxyandrost-5-en-17-one. The new analogs are characterized by the ability to increase intestinal calcium transport, increase serum calcium and phosphate concentrations and to increase the deposition of these minerals in bones. These compounds will find a ready application as substitutes for natural 1.alpha.,25-dihydroxycholecalciferol in the treatment of disease states characterized by metabolic calcium and phosphate deficiencies. Exemplary of such disease states are the following: osteomalacia, osteoporosis, rickets, osteitis fibrosa cystica, renal osteodystrophy, osteosclerosis, anti-convulsant treatment, osteopenia, fibrogenesis-imperfecta ossium, secondary hyperparathyrodism, hypoparathyroidism, hyperparathyroidism, cirrhosis, obstructive jaundice, drug induced metabolism, medullary carcinoma, chronic renal disease, hypophosphatemic VDRR, vitamin D-dependent rickets, sarcoidosis, glucocorticoid antagonism, malabsorption syndrome, steatorrhea, tropical sprue, idiopathic hypercalcemia and milk fever.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 14 OF 16 USPATFULL
AN 86:2096 USPATFULL
TI 23,23-Difluoro-25-hydroxy-vitamin D.sub.3 and process for preparing same
IN DeLuca, Hector F., Madison, WI, United States
Tanaka, Yoko, Madison, WI, United States
Ikekawa, Nobuo, Tokyo, Japan
Kobayashi, Yoshiro, Tokyo, Japan
PA Wisconsin Alumni Research Foundation, Madison, WI, United States (U.S. corporation)
PI US 4564474 860114
AI US 84-639776 840813 (6)
DCD 20020219
RLI Continuation-in-part of Ser. No. US 83-524269, filed on 18 Aug 1983
DT Utility
EXNAM Primary Examiner: Roberts, Elbert L.
LREP Bremer, Howard W.
CLMN Number of Claims: 3
ECL Exemplary Claim: 1,3
DRWN No Drawings
LN.CNT 489
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides new derivatives of vitamin D, 23,23-difluoro-25-hydroxycholecalciferol and the acylates thereof, a method for preparing said compounds and various new intermediates utilized in such process.

The derivative compounds are characterized by vitamin D-like activity as evidenced by their ability to increase intestinal calcium transport and serum calcium. The compounds are further characterized by resistance to hydroxylation at C-23, which is recognized as an essential metabolic step to the inactivation of vitamin D. The compounds should, therefore, provide vitamin D-like activity of greater time duration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 15 OF 16 USPATFULL
AN 82:22686 USPATFULL
TI 24-Cyclopropylcholene-3.beta., 22-diols and esters thereof
IN Chorvat, Robert J., Arlington Heights, IL, United States
PA G. D. Searle & Co., Skokie, IL, United States (U.S. corporation)
PI US 4329295 820511
AI US 81-278276 810629 (6)
DT Utility

EXNAM Primary Examiner: Roberts, Elbert L.
LREP Drehkoff, W. Dennis; Passe', James G.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 259
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB 24-Cyclopropylcholene-3.**beta**., 22-diols and esters thereof which control serum **cholesterol** levels and their preparation are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L29 ANSWER 16 OF 16 USPATFULL
AN 81:23334 USPATFULL
TI Contraceptive methods and compositions
IN Burck, Philip J., Indianapolis, IN, United States
Zimmerman, Ronald E., Danville, IN, United States
Thakkar, Arvind L., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4264578 810428
AI US 80-138394 800408 (6)
RLI Continuation-in-part of Ser. No. US 79-57931, filed on 16 Jul 1979, now abandoned which is a continuation of Ser. No. US 78-973252, filed on 26 Dec 1978, now abandoned
DT Utility
EXNAM Primary Examiner: Rose, Shep K.
LREP Rowe, James L..; Whale, Arthur R.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 602
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Introduction of a pharmaceutically acceptable non-toxic cation salt of a sterol sulfate into the uterine lumen or vaginal cavity prevents conception. Potassium or pyridinium .beta.-sitosteryl sulfate is preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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